

Cover Page for Protocol

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NCT number	NCT05350969
Sponsor trial ID:	CDR132L-P2-01
Official title of study:	Phase 2, Multicenter, Randomized, Parallel, 3-arm, Placebo-controlled Study to Assess Efficacy and Safety of CDR132L in Patients with Reduced Left Ventricular Ejection Fraction ($\leq 45\%$) After Myocardial Infarction (HF-REVERT)
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TITLE PAGE

Protocol Title: Phase 2, Multicenter, Randomized, Parallel, 3-arm, Placebo-controlled Study to Assess Efficacy and Safety of CDR132L in Patients with Reduced Left Ventricular Ejection Fraction ($\leq 45\%$) After Myocardial Infarction (**HF-REVERT**)

Protocol Number: CDR132L-P2-01

Amendment Number: 3.1

Product: CDR132L

Short Title: Phase 2 Study to Assess Efficacy and Safety of CDR132L in Patients with Reduced Left Ventricular Ejection Fraction ($\leq 45\%$) After Myocardial Infarction (**HF-REVERT**)

Study Phase: 2

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IRAS: 1006514

Date of Protocol Amendment 3.1: 16 May 2023

*Redacted protocol
includes redaction of personal identifiable and company
confidential information.*

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

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[Redacted]
Name des Unterzeichners: [Redacted]
Signiergrund: Ich genehmige dieses Dokument
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2023-05-19 | 01:57:57 PDT

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Date

Investigator Agreement Page is provided in [Appendix 6](#). The Investigator should retain the original in the study site study files and return a copy to the Sponsor or Contract Research Organization for archiving.

Each Investigator should be sent a copy of the Investigator Agreement Page for completion. Signatures are obtained after the Sponsor has finalized and approved the protocol.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY			
Document	Date	Substantial	Region
Amendment 3.1	16-May-2023	No	Global
Amendment 3	30-March-2023	No	Global
Amendment 2	03-November-2022	Yes	UK, GR
Amendment 1	15-July-2022	Yes	Global
Original Protocol	07-December-2021		

Amendment 3.1 (16-May-2023)

Administrative change of the description on Amendment 2 to be in line with the summary of changes table.

Amendment 3 (30-March-2023)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

Following 9 months of recruitment the sponsor sees the need to clarify and adapt the protocol to reflect health care reality. Thus, the following changes were made to take burden from patients and facilitate work at the study sites. Furthermore, this amendment will harmonize the study protocol across all participating countries.

Section Number	Description of Change	Brief Rationale
MAJOR REVISIONS		
1.1, 3.0, 8.2.5.2	Killip classification removed as secondary endpoint.	Killip assessment is not designed to assess changes in heart health; it will therefore be assessed only at baseline for risk stratification.
CCI		
5.2	“and clinical relevant” added to exclusion criterion 19.	Wording removed to reflect current clinical practices regarding COVID-19.
8.4.1	Time Period and Frequency for Collecting AE and SAE Information section reworded	New wording to clarify differentiation between MI

Section Number	Description of Change	Brief Rationale
		related and non-MI related events prior to dosing.
Appendix 2	“or the patient’s legally authorized representative” removed	Wording removed as patients with legal representative will not be included in the study.
Appendix 5	“For WOCBPs in clinical trials” added to table 6	Clarification in line with cited guidance.
MINOR REVISIONS		
1.1, 4.2	Change from 60 to 70 investigators	Increase of site number
1.3	Urine assessments deleted at EoS; Killip assessments removed at visit 5, 6, and 7.	Not required as safety lab will not be analyzed; removal of patient burden; Killip class assessment removed in line with CCI endpoint removal.
5.1	Women of non-childbearing potential added in inclusion criterion 1 to be in line with exclusion criterion 1	Clarification: previous wording is unclear as WoNCBP were only mentioned in exclusion criterion 1.
5.1	“(if sites use the SoC sample or the local laboratory sample for eligibility confirmation, no additional sample laboratory assessment is needed)” removed from inclusion criterion 8.	Misleading wording removed.
5.1	“or angiography (if no indication for stent placement or balloon procedure)” added to inclusion criterion 9	Additional wording needed to clarify the intention of inclusion criterion 9 as PCI would only refer to intervention.
5.2	“the Screening Period” replaced by “MI index event” in exclusion criterion 3.	Previous wording led to exclusion of eligible patients due to misunderstanding.
5.2	“randomization” replaced by “prior to first dose” in exclusion criterion 7.	Clarification as previous wording led to some misunderstanding.
5.2	Exclusion criterion 23	Wording adjusted to clarify period of prohibited concomitant medication.
6.1	“or on the same day” added	Wording added to allow for more flexibility at sites.
6.5.1	Prohibited Therapies section	Clarifications and deleting redundancies with exclusion criteria.
7.1	Discontinuation of Study Treatment	Clarification about discontinuation criteria; and planned follow-up for discontinued patients.
7.2	References to COVID-19 removed from discontinuation	Removal to reflect current knowledge and clinical reality.

Section Number	Description of Change	Brief Rationale
8.2.3	“either on paper or digitally” added	Clarification that both versions can be used.
CCI		
8.4.5	“(in female partners of male patients)” removed	Wording deleted as redundant in line with in- and exclusion criteria.
Throughout the protocol as applicable	Editorial changes including revision related to headings, formatting, grammar, footnotes, numbering, consistency of terms (i.e., changed center to site), abbreviations, spelling, punctuation, wordsmithing, and typos	For clarity and improve readability.

Amendment 2 (03-November-2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This Amendment reflects adaptations to include trial sites in the UK and removes information regarding IMP handling and storage that is more clearly explained in the Pharmacy Manual.

Section Number	Description of Change	Brief Rationale
MAJOR REVISIONS		
6.2	Replacement of preparation instruction with reference to pharmacy manual; change of storage temperature range.	To avoid misunderstandings between protocol and pharmacy manual and reflect current stability data.

Amendment 1 (15-July-2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

For clarity and safety reasons, the following changes were made as described below.

Section Number	Description of Change	Brief Rationale
MAJOR REVISIONS		
Section 1.3 Schedule of Activities	Added footnote “a,” stating that events and diseases will be recorded for up to 6 months prior to screening. COVID-19 infections and vaccinations will be recorded regardless of their time of	To improve clarity and provide more information

Section Number	Description of Change	Brief Rationale
	occurrence. Clarified pre-dose and post-dose assessment for Day 1	
Section 4.3.1 Justification for Selection of Planned CDR132L Doses	Added justification for maximum exposure	To provide more information
Section 5.3 Lifestyle Recommendations	Simplified lifestyle recommendations and moved recommendation regarding caffeine- or xanthine-containing products and alcohol in Section 8	To improve clarity and provide flexibility regarding local recommendations and guidelines
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	Clarified that blinding of study treatment is to occur until all patients have completed Month 6. Clarified that investigational treatment and placebo will be masked. Added Section 6.3.1 Emergency Unblinding	To improve clarity and provide more information
Section 7 Discontinuation of Study Treatment and Patient Discontinuation/Withdrawal	Clarified criterion for discontinuation related to abnormal liver function. Added criteria for discontinuation related to renal damage and hypersensitivity to CDR132L. Clarified patient discontinuation/withdrawal. Added Section 7.4 Criteria for Stopping the Study	To improve clarity and provide more information
Section 8 Study Assessments and Procedures	Added Section 8.1 Medical History	To provide more information
Section 9 Statistical Considerations	Added Section 9.3.1 Baseline	To provide more information
Appendix 2	Removed legally authorized representative	For consistency with the exclusion criteria
Appendix 3	Updated Table 5	To improve clarity and provide more information
Appendix 4	Clarified assessment of causality	To improve clarity
MINOR REVISIONS		
Throughout the protocol as applicable	Changed Extension Period to Prolonged Follow-up Period	To improve clarity
Throughout the protocol as applicable	Removed efficacy-related	To improve clarity
Throughout the protocol as applicable	Changed original protocol to protocol amendment 1.	To clarify that this is the first amendment to the protocol
Throughout the protocol as applicable	Editorial changes including revision related to headings, formatting, grammar, footnotes, numbering, consistency of terms (i.e., changed center to site), abbreviations, spelling, punctuation, wordsmithing, and typos	For clarity and improve readability

Abbreviations: COVID-19 = coronavirus disease 2019.

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: Phase 2, Multicenter, Randomized, Parallel, 3-arm, Placebo-controlled Study to Assess Efficacy and Safety of CDR132L in Patients with Reduced Left Ventricular Ejection Fraction ($\leq 45\%$) After Myocardial Infarction (**HF-REVERT**)

Short Title: Phase 2 Study to Assess Efficacy and Safety of CDR132L in Patients with Reduced Left Ventricular Ejection Fraction ($\leq 45\%$) After Myocardial Infarction (**HF-REVERT**)

Rationale:

Several completed pre-clinical studies assessing the pharmacokinetics (PK), pharmacology, safety pharmacology, and toxicological profile of CDR132L have demonstrated that the safety profile is adequate to progress with clinical development. The non-clinical data supported the clinical drug regime in the recently-completed first-in-human (FIH) study in 28 patients with stable heart failure (HF) (New York Heart Association [NYHA] class I to III) of ischemic origin. This study determined the effects of 4 dose levels: CCI, 1, 2, and CCI mg/kg of CDR132L administered intravenously (IV) on Days 1 and 28 as an add-on to Standard of Care (SoC). All dose levels were found to be safe and well tolerated with minimal related-treatment-emergent adverse events (TEAEs) and no clinically relevant changes in laboratory parameters, physical examination findings, vital signs, echocardiography (ECHO), or electrocardiogram (ECG). CCI

. Based on pharmacodynamic and safety considerations, 5 and 10 mg/kg were selected as the dose levels for this Phase 2 study.

This Phase 2 study aims to assess the efficacy and safety of CDR132L 5 mg/kg and 10 mg/kg, given as 3 single IV doses administered 28 days apart as an add-on to SoC therapy, in a larger cohort of patients (N = 280) with HF and reduced left ventricular ejection fraction (LVEF) ($\leq 45\%$) after myocardial infarction (MI) with a follow-up of 10 months.

Objectives and Endpoints

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To assess the efficacy of 2 dose levels (5 and 10 mg/kg) of CDR132L compared with placebo administered in 3 single IV doses given 28-days apart in patients with reduced LVEF $\leq 45\%$ after MI (STEMI or NSTEMI) as add-on therapy to SoC treatment 	<ul style="list-style-type: none"> Percent change from baseline (screening to occur at least 3 days (up to 14 days) after MI diagnosis as measured by ECHO [central laboratory]) in LVESVI at Month 6

Objectives	Endpoints
Secondary	
<ul style="list-style-type: none"> To assess the safety of 2 dose levels (5 and 10 mg/kg) of CDR132L compared with placebo 	<ul style="list-style-type: none"> Frequency of adverse events and abnormalities in clinical laboratory assessments, vital signs, physical examination, ECGs, and urinalysis
<ul style="list-style-type: none"> To assess the effects of CDR132L compared with placebo on cardiac function 	<ul style="list-style-type: none"> Change from baseline LVEF (absolute/relative) at Months 3, 6, and 12 Change from baseline LVESVI at Month 3 (absolute/relative), Month 6 (absolute), and Month 12 (absolute/relative)
<ul style="list-style-type: none"> To assess the effects of CDR132L compared with placebo on efficacy-related biomarkers 	<ul style="list-style-type: none"> Change from baseline in absolute/relative troponin T (ng/L) at Months 3, 6, and 12 Change from baseline in absolute/relative values over time for the following efficacy-related biomarkers: <ul style="list-style-type: none"> N-terminal pro B-type natriuretic peptide (NT-proBNP)
<ul style="list-style-type: none"> To assess the effects of CDR132L compared with placebo on patient well-being 	<ul style="list-style-type: none"> Well-being as evaluated by change from baseline at Months 6 and 12 in the following parameters: <ul style="list-style-type: none"> Mean KCCQ score and mean scores of subdomains (symptom burden, physical limitation, and quality of life)
Exploratory	
<ul style="list-style-type: none"> CCI [REDACTED] 	<ul style="list-style-type: none"> CCI [REDACTED]
<ul style="list-style-type: none"> CCI [REDACTED] 	<ul style="list-style-type: none"> CCI [REDACTED]
<ul style="list-style-type: none"> CCI [REDACTED] 	<ul style="list-style-type: none"> CCI [REDACTED]

Abbreviations: ECG = electrocardiogram; ECHO = echocardiography; CCI [REDACTED]; IV = intravenously; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; MI = myocardial infarction; CCI [REDACTED]; NSTEMI = non-ST-segment elevation myocardial infarction; CCI [REDACTED]; SoC = Standard of Care; STEMI = ST-segment elevation myocardial infarction.

Overall Design:

This is a Phase 2, multicenter, randomized, parallel, 3-arm, placebo-controlled study to assess efficacy and safety of CDR132L in patients with reduced LVEF ($\leq 45\%$) after MI. This study consists of a Screening Period (to occur at least 3 days after MI diagnosis), a 6-month Double-blind Period, and a 6-month Prolonged Follow-up Period with the End of Study (EOS) Visit at Day 360/Month 12.

Patients will be screened to determine eligibility at least 3 days after MI diagnosis; all eligibility criteria must be confirmed no later than 14 days after MI diagnosis. Screening and dosing can be done in an inpatient (in case patients are hospitalized due to MI or HF) or outpatient setting. A total of approximately 280 unique individual patients will be randomly assigned to the 3 treatment groups in 1:1:1 ratio, with approximately 90 patients in each treatment group. Groups 1 and 2 will include patients who will receive CDR132L 5 mg/kg or 10 mg/kg IV, respectively. Patients in the placebo group (Group 3) are included for evaluation of efficacy and safety.

On Day 1 (preferably within one day after randomization but no later than 4 days after randomization), patients will receive CDR132L 5 mg/kg, CDR132L 10 mg/kg, or placebo IV. The second IV dose of the patient's assigned treatment will be administered on Day 29 ± 2 days, and the third IV dose on Day 57 ± 2 days. For doses administered in an outpatient setting, the patient should be observed for at least 30 minutes after dosing.

All patients will be required to attend the study visits as described in the Schedule of Activities. All patients will receive SoC therapy after MI and eventually for HF. CDR132L or placebo will be administered as add-on therapy to the SoC treatment. All patients will be followed for 10 months for efficacy and safety assessments. Overall, study duration for each patient will be approximately 12 months. A Data Safety Monitoring Board will closely supervise all data to monitor the safety of all patients.

Number of Investigators and Study Sites:

Approximately 70 Investigators and study sites are expected to participate in this study.

Number of Patients:

It is planned that approximately 280 patients will be enrolled/randomized into the study in a 1:1:1 ratio (approximately 90 patients each, in 5 mg/kg, 10 mg/kg, and placebo groups). Assuming 10 patients will not be evaluable, it is anticipated that 270 patients will be evaluable (equally distributed among groups).

Treatment Groups and Duration:

Eligible patients will be randomized to receive CDR132L 5 mg/kg (Group 1), CDR132L 10 mg/kg (Group 2), or placebo (Group 3) IV; N = 90 patients per group. Patients will receive CDR132L 5 mg/kg, CDR132L 10 mg/kg, or placebo on Day 1. The second IV dose of the patient's assigned treatment will be administered on Day 29 $\pm$ 2 days, and the third IV dose on Day 57 $\pm$ 2 days.

Statistical Methods:

The primary endpoint is defined as percent (%) change from baseline left ventricular end-systolic volume index (LVESVI) at Month 6 compared with baseline (after reperfusion, before treatment start) on top of SoC as measured by ECHO (central laboratory).

For the sample size calculation, the two-sample t-test is used. The test level is set to 2.5% (one-sided). Assumptions are displayed below.

Left ventricular end-systolic volume index	Mean (change in %)	Standard deviation (%)
Placebo response	1	9
10 mg/kg	6	9
5 mg/kg	5	9
N = 90 per group	Step 1	96.0%
	Step 2	84.3%
	Overall	80.9%

Step 1 (10 mg/kg versus placebo):

A sample size of 90 in each group will have 96.0% power to detect a difference in means of 5 (the difference between a Group 1 mean, μ_1 , of 6 and a Group 2 mean, μ_2 , of 1) assuming that the common standard deviation is 9 using a 2-group t-test with a 2.5% one-sided significance level.

Step 2 (5 mg/kg versus placebo):

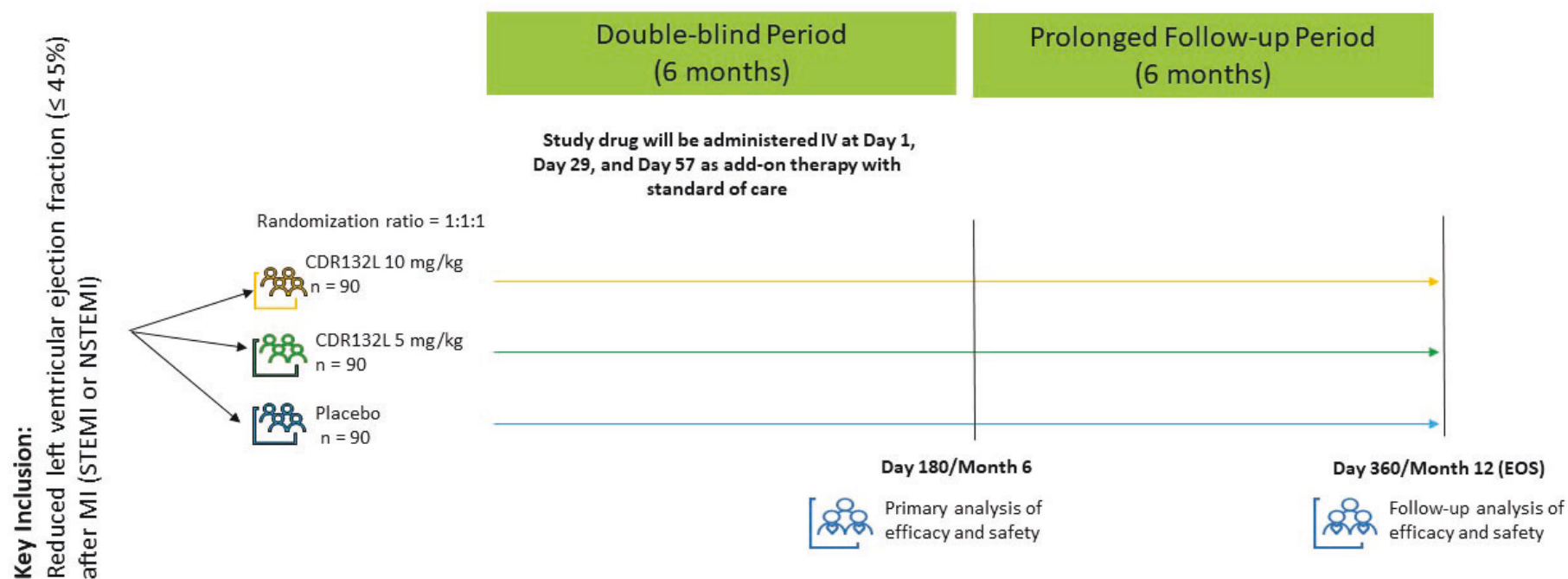
A sample size of 90 in each group will have 84.33% power to detect a difference in means of 4 (the difference between a Group 1 mean, μ_1 , of 5 and a Group 2 mean, μ_2 , of 1) assuming that the common standard deviation is 9 using a 2-group t-test with a 2.5% one-sided significance level.

Including 90 patients per group (270 total) will lead to a power of 96.0% for the first step (10 mg/kg vs placebo, difference in means of 5) and 84.3% for the second step (5 mg/kg vs placebo, difference in means of 4) of the hierarchical test procedure, resulting in an overall power of 80.9%. Ten additional patients should be included to compensate for early dropouts.

Data Safety Monitoring Board: Yes; [Section 9.5](#)

1.2 Schema

Figure 1 Study Schema



Abbreviations: ECHO = echocardiography; EOS = end of study; IV = intravenous; LVEF = left ventricular ejection fraction; MI = myocardial infarction; n = number of patients; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

Note: To be eligible, patients must have LVEF $\leq 45\%$ as measured by ECHO performed at least 3 days after diagnosis of MI (STEMI or NSTEMI). Eligible patients who receive study drug will also have an ECHO performed at Day 90/Month 3, Day 180/Month 6, and Day 360/Month 12.

1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedures	Screening Period (To occur at least 3 days after MI diagnosis)	Double-blind Period (Day 1 to Day 180/Month 6)							Prolonged Follow-up Period (6 months)
		Study Drug Treatment (Day 1, Day 29, and Day 57)					Follow-up		
Visit	Screening Period (To occur at least 3 days after MI diagnosis)	Randomization (To occur no later than 14 days after MI diagnosis)	1	2	3	4	5	6	EOS/ET
Study Day			Day 1 (pre-dose)	Days 2 to 5	Day 29	Day 57	Day 90	Day 180	Day 360
Window (days)					± 2	± 2	± 7	± 7	± 7
Month					Month 1	Month 2	Month 3	Month 6	Month 12
Informed consent	X								
Demographic data and medical history ^a	X ^a								
Inclusion/exclusion criteria	X								
Randomization		X							
Study drug administration ^b			X ^b		X	X			
Prior/concomitant medications	X		X	X	X	X	X	X	X
EFFICACY									
Echocardiography ^c	X ^c						X	X	X
KCCQ	X						X	X	X
hs-cTn	X		X	X	X	X	X	X	X
NT-proBNP	X ^d		X	X	X	X	X	X	X
SAFETY									
Adverse event assessments	X		X	X	X	X	X	X	X

Procedures	Screening Period (To occur at least 3 days after MI diagnosis)	Double-blind Period (Day 1 to Day 180/Month 6)							Prolonged Follow-up Period (6 months)
		Study Drug Treatment (Day 1, Day 29, and Day 57)					Follow-up		
Visit		Randomization (To occur no later than 14 days after MI diagnosis)	1	2	3	4	5	6	EOS/ET
Study Day			Day 1 (pre-dose)	Days 2 to 5	Day 29	Day 57	Day 90	Day 180	Day 360
Window (days)					± 2	± 2	± 7	± 7	± 7
Month					Month 1	Month 2	Month 3	Month 6	Month 12
Injection site reaction monitoring			X (post-dose)		X	X			
Physical examination	X		X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X
12-lead electrocardiogram	X		X		X	X	X	X	X
Body weight	X			X	X	X	X	X	X
Hematology, biochemistry, coagulation ^c	X		X	X	X	X	X	X	
Urinalysis ^c	X		X		X		X	X	
EXPLORATORY EFFICACY									

CCI

Procedures	Screening Period (To occur at least 3 days after MI diagnosis)	Double-blind Period (Day 1 to Day 180/Month 6)							Prolonged Follow-up Period (6 months)
		Study Drug Treatment (Day 1, Day 29, and Day 57)					Follow-up		
Randomization (To occur no later than 14 days after MI diagnosis)		1	2	3	4	5	6	EOS/ET	
		Day 1 (pre-dose)	Days 2 to 5	Day 29	Day 57	Day 90	Day 180	Day 360	
				± 2	± 2	± 7	± 7	± 7	
				Month 1	Month 2	Month 3	Month 6	Month 12	
Visit									
Study Day									
Window (days)									
Month									
CCI									
Immunogenicity ^e			X		X	X		X	

Abbreviations: COVID-19 = coronavirus disease 2019; ECHO = echocardiography; ED = emergency department; EOS = end of study; ET = early termination; hs-cTn=high-sensitivity cardiac troponin; IV = intravenous; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro B-type natriuretic peptide; CCI

Note: All blood samples should be collected pre-dose at dosing days.

- Events and diseases will be recorded for up to 6 months prior to screening. COVID-19 infections and vaccinations will be recorded regardless of their time of occurrence.
- On Day 1 (preferably within one day after randomization but no later than 4 days after randomization) patients will receive CDR132L 5 mg/kg, CDR132L 10 mg/kg, or placebo IV. The second IV dose of the patient's assigned treatment will be administered on Day 29 ± 2 days, and the third IV dose on Day 57 ± 2 days. For doses administered in an outpatient setting, the patient should be observed for at least 30 minutes after dosing.
- The screening ECHO will be performed at least 3 days after MI diagnosis; all eligibility criteria must be confirmed no later than 14 days after MI diagnosis.
- At screening, sample is to be collected as early as possible preferably on the same day as the ECHO. NT-proBNP values required for eligibility confirmation may be collected at any time post MI either through medical history (e.g., site has collected it as SoC once the patient came to the hospital), through a local laboratory assessment, or by sending a sample to the central laboratory (if sites use the SoC sample or the local laboratory sample for eligibility confirmation, no additional sample for central laboratory assessment is needed).
- See [Appendix 3](#) for more information.

2.0 INTRODUCTION

CDR132L is a synthetic antisense oligonucleotide (ASO) and a selective inhibitor of microRNA-132-3p (miR-132). miR-132 in cardiomyocytes is a central switch affecting the expression of genes that are crucially involved in maladaptive cardiac remodeling, transformation, and pathological cardiac growth (hypertrophy), contributing to adverse cardiac remodeling and heart failure (HF).¹⁻⁵ Aberrant expression of miR-132 in cardiac cells is causally associated with cardiac remodeling and HF progression.¹⁻⁶

The characteristic common pathological feature in HF after myocardial infarction (MI) is adverse structural remodeling of the left ventricle. Dysfunctional left ventricular remodeling that occurs in response to mechanical stress and neurohormonal activation after an MI was initially considered irreversible, with only a decrease in heart size possible by therapies such as angiotensin-converting enzyme inhibitors, beta-blockers, and cardiac synchronization therapy. However, reverse remodeling, a process by which the failing myocardium normalizes chamber geometry and function with correction of molecular and transcriptional abnormalities, is now being recognised.⁷ Blocking aberrant miR-132 expression by the selective ASO inhibitor CDR132L is suited to reverse MI-related adverse cardiac effects and restore normal cellular function in cardiomyocytes, contributing to improved cardiac function in stable ischemic HF patients.^{2,3,8}

The global burden of HF is significant, with an estimated prevalence of 64.34 million cases contributing to 9.91 million years lost to disability.⁹ Heart failure complicating acute MI is common and is a powerful predictor of death.¹⁰ The incidence of HF among patients hospitalized for MI varies between 14% and 36%.^{11,12} Inhibition of miR-132 effectively prevents progression of HF in an animal model of the disease,¹³ and translational in vitro and in vivo studies have demonstrated the safety, tolerability, and efficacy of CDR132L in HF.^{3,2} In addition, a recent first-in-human (FIH) study exploring a range of doses (CC1 mg/kg) reported CDR132L to be safe and well tolerated in patients with stable ischemic HF as an add-on therapy to Standard of Care (SoC), and supports the progression to the next stage of clinical development.⁴

2.1 Study Rationale

Several completed pre-clinical studies assessing the pharmacokinetics (PK), pharmacology, safety pharmacology, and toxicological profile of CDR132L have demonstrated that the safety profile is adequate to progress with clinical development. The non-clinical data supported the clinical drug regimen in the recently-completed FIH study in 28 patients with stable HF (New York Heart Association [NYHA] class I to III) of ischemic origin.⁴ This study determined the effects of 4 dose levels: CC1, 1, 2, and CC1 mg/kg of CDR132L administered intravenously (IV) on Days 1 and 28 as an add-on to SoC. All dose levels were found to be safe and well tolerated with minimal treatment-related treatment-emergent adverse events (TEAEs) and no clinically relevant changes in laboratory parameters, physical examination findings, vital signs, echocardiography (ECHO),

or electrocardiogram (ECG). Pharmacokinetic analysis supported a good safety profile, with no accumulation, in line with a short half-life ($T_{1/2}$) of around 4 hours, a restricted volume of distribution, and a high degree of dose linearity with regards to maximum plasma concentration (C_{max}). Dose-normalized area under the curve suggested a greater than dose-proportional increase in exposure with increasing dose. The Phase 1b FIH study therefore supports ongoing clinical assessment of CDR132L in the planned Phase 2, proof-of-concept study. Based on pharmacodynamic (PD) and safety considerations, 5 and 10 mg/kg were selected as the dose levels for this Phase 2 study.

This Phase 2 study aims to assess the efficacy and safety of CDR132L 5 mg/kg and 10 mg/kg, given as 3 single IV doses administered 28 days apart as an add-on to SoC therapy, in a larger cohort of patients (N = 280) with HF and reduced LVEF ($\leq 45\%$) after MI with a follow-up of 10 months.

2.2 Background

Current state-of-the-art HF pharmacotherapy is largely focused on symptomatic management; that is, mainly on reducing cardiac load by reducing neurohormonal overdrive and volume retention. The recommended guideline-directed medical therapy (GDMT) includes diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, aldosterone antagonists, angiotensin receptor neprilysin inhibitors, and ivabradine. Mechanical circulatory support and heart transplant is reserved for the treatment of patients with severe HF with reduced ejection fraction (EF) who have failed GDMT.¹⁴ Novel, efficient, disease-halting therapeutics that reduce mortality and hospitalization are urgently needed to offer curative hope for these patients. CDR132L is a unique miRNA-based next generation drug in HF, with the potential to improve patient care and reduce the financial burden of HF care.

The mechanism of action (MoA) of CDR132L has the following key elements forming the basis of its role as a novel drug in HF: a) normalization of aberrant cardiac miR-132 levels, b) normalization of calcium signaling and contractility as well as cardiac function, c) improvement in cardiac autophagy and homeostasis, and d) attenuation of maladaptive cardiac remodeling (reducing pathological cardiomyocyte growth and cardiac fibrosis).¹⁻⁵

2.2.1 Overview of Non-clinical Studies

CDR132L has undergone an extensive non-clinical safety evaluation including safety pharmacology and repeat-dose toxicity studies. Additional safety information is available from a large proof-of-concept study in CCI in a clinically relevant model of post MI HF.

CDR132L was well tolerated at 1, 5, and 10 mg/kg in the proof-of concept study in CCI. No acute effects on the central nervous system (CNS), CV, and respiratory system have been observed in Good Laboratory Practices (GLP)-compliant safety pharmacology studies in CCI. In a GLP-compliant CCI toxicity study in CCI, the animals received 2 slow

intravenous bolus injections of 0 (vehicle), 4, 20 and 100 mg/kg CDR132L on Days 1 and 28. Additional animals from the control and high-dose group were subjected to a 4-week recovery period after completion of the treatment period. In the main groups, there were slightly decreased red blood cell (decreased hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin) and coagulation parameters (decreased prothrombin time and partial thromboplastin time) at 100 mg/kg CDR132L, which may be treatment-related. Mildly but significantly increased alanine aminotransferase (ALT) and aspartate aminotransferase levels at 100 mg/kg may suggest an adverse effect of CDR132L on the liver, however, there was no morphological correlate, and the effects reversed during a 4-week recovery period. Slightly increased creatinine values indicating impairment of renal function were found in the 100 mg/kg dose group. Macroscopic findings were noted in the kidney in animals from the 100 mg/kg dose group. The kidneys were slightly paler compared with kidneys from control animals showing a light brown parenchyma. Relative kidney weights were increased at the end of the treatment period in female animals and at the end of the recovery period in male animals treated with 100 mg/kg. Relative liver weights were increased at the end of the recovery period in animals treated with 100 mg/kg. Increased kidney and liver weights likely represent the presence of high concentrations of the study drug and the water that is required to keep it hydrated. Histological examination revealed treatment-related findings in the kidney in the form of basophilic granules in the cytoplasm of the tubular epithelium, degeneration of the tubular epithelium, dilation of tubules, and regeneration of tubules. The basophilic granules within the cytoplasm of the tubular epithelium were dose-dependent and occurred at 20 and 100 mg/kg and were still observable in the high-dose animals at the end of the recovery period. Very slight to slight degeneration of the tubular epithelium, very slight dilation and regeneration of tubules were only detected in the high-dose group. The incidence of very slight to slight degeneration of the tubular epithelium was interpreted as adverse. The very slight dilation and regeneration of tubules were considered to be the consequence of the degenerative effect on the tubular epithelium observed. The no-observed-adverse-effect-level (NOAEL) in this study was considered to be 20 mg/kg, due to effects observed in clinical chemistry and histopathological effects on the kidneys at 100 mg/kg.

In a GLP-compliant **CCI** toxicity study in **CCI**, the animals received 6 slow IV bolus injections of 0 (vehicle), 10, 20 and 60 mg/kg CDR132L every 4 weeks. Additional animals from the control and high-dose group were maintained for a 3-month recovery period after completion of the treatment period. Six animals from the high-dose group (60 mg/kg) were found dead or were killed moribund in the course of the study. Body weights were significantly lower in animals from the high-dose group and body weight gains were reduced in males from the high-dose group. Food consumption was decreased in males and females from the high-dose group. Reduced red blood cell counts observed in males and females at 60 mg/kg were suggestive of anemia. Increased laboratory parameters reflecting renal function i.e., creatinine and urea, plasma electrolytes, indicated a treatment-related effect on the kidney. Pronounced hemolysis, which was observed primarily in the males from the high-dose group, was considered to be secondary to the renal

impairment, as increased urea levels lead to hemolysis during the cause of renal anemia. In addition, hyperkalemia, hyperphosphatemia, hypocalcemia, decreased albumin, increased globulin as well as strongly increased cholesterol and triglyceride levels were observed, which were considered secondary to the kidney effects. Quantitative urinalysis revealed decreased osmolality in the high-dose group and semiquantitative urinalysis results revealed increased leukocytes and urinary blood in CCI of either sex, which again suggested a treatment-related effect on the kidney. The thymus was slightly to moderately smaller in some females from the high-dose group. The kidneys were slightly to moderately enlarged in animals from the high-dose group. Histopathologically, treatment-related effects were observed in the kidney, liver, and bone marrow. Kidney findings consisted of basophilic granules within the cytoplasm of the tubular epithelium, which were dose-dependent and occurred in male and female animals from the low-, mid-, and high-dose and were still observable in male and female animals from the high-dose recovery group. In the absence of any degenerative findings, basophilic granules in the kidneys were regarded as non-adverse. Findings of degeneration of the tubular epithelium, increased infiltration of mixed inflammatory cells and interstitial fibrosis, which were significantly increased in males and partially in females from the high-dose main study group and in male and female animals from the high-dose recovery group, were interpreted as adverse. Dilatation of tubules, intraluminal hyaline casts in the tubules and regeneration of tubules were interpreted to be the consequence of the degeneration of the tubular epithelium. These changes were significantly increased in the male and female animals from the high-dose main study and recovery groups. The findings of the kidneys in the animals from the high-dose group progressed during the recovery period developing into more severe changes. Treatment-related finding within the liver consisted of basophilic granules within cellular cytoplasm. This finding was regarded as an adaptive change. Treatment-related finding within the bone marrow consisted of decreased erythroid cellularity in few animals. This change was interpreted to be secondary to the kidney changes most likely due to decreased erythropoietin production. The NOAEL in this study was considered to be the mid-dose (20 mg/kg).

In a GLP-compliant CCI toxicity study in CCI, the animals received 0 (vehicle), 4, 20, and 40 mg/kg CDR132L on Days 1 and 28 by a 15-minute IV infusion. No signs of toxicity were observed in this study and thus the NOAEL was determined to be 40 mg/kg, the highest dose tested. Adequate systemic exposure to CDR132L was confirmed by toxicokinetic assessments.

In a GLP-compliant CCI toxicity study in CCI, the animals received nine 15-minute IV infusions at dose levels of 0 (vehicle) 4, 20, or 40 mg/kg every 4 weeks. Additional animals from the control and high-dose group were maintained for a 3-month recovery period after completion of the treatment period. The following findings were noted:

- At macroscopic examination, enlarged and discolored kidneys were observed in 1 out of 4 male and 2 out of 4 female animals treated with 40 mg/kg CDR132L. Histopathologically, there were test item-related microscopic changes in the kidneys in the form of basophilic

epithelial swelling, tubular dilatation, tubular hyaline casts, tubular neutrophilic infiltration, tubular fatty infiltration, and in cervical and mesenteric lymph nodes (foamy macrophage) in male and female animals treated with 20 or 40 mg/kg.

- Microscopic changes were also noted in the testes in the form of increased severity of tubular atrophy, correlating with the decreased relative and absolute testes weights, and epididymides in the form of oligospermia, immature germ cells, sperm granuloma and/or aspermia in male animals treated with 20 or 40 mg/kg.
- Histopathological examination of recovery animals previously treated with 40 mg/kg still revealed microscopic changes in the kidneys in the form of minimal tubular epithelial basophilic swelling, in the cervical and mesenteric lymph nodes in the form of foamy macrophages, in the testes and the epididymides in the form of tubular atrophy and the presence of immature germ cells.

However, a trend towards full recovery was noted for the findings observed in the kidneys, epididymides, and testes at the end of the treatment period as a clear decrease was noted for both the incidence and the severity of the changes. A trend towards recovery was also noted for the microscopic changes in the cervical and mesenteric lymph nodes as the severity of the finding declined compared with the main study animals. At 20 mg/kg, microscopic changes were confined to mild to moderate tubular basophilic epithelial swelling in the kidneys and foamy macrophages in the cervical and mesenteric lymph nodes, which, in the absence of any degenerative findings, were regarded as non-adverse. The changes in the kidney and lymph nodes observed at 20 and 40 mg/kg CDR132L are likely attributable to the presence of the test item as described in the literature for CCI and other species following treatment with antisense oligonucleotides.^{15,16} Microscopic findings noted in the testes in the form of tubular atrophy at 20 and 40 mg/kg CDR132L and correlating findings in the epididymides are known to be common spontaneous findings in CCI which are often accompanied by decreased testes weights. For example, it has been reported that tubular atrophy is observed in more than 70% of naïve CCI with similar findings observed in the epididymides in more than 20% of naïve CCI.¹⁷

Although the number of animals examined at the end of the treatment period was low (4 males per group), which hampers the interpretation of the findings, the severity of the testes atrophy and the incidence and severity of the accompanying changes in the epididymides at 20 and 40 mg/kg CDR132L revealed a slight dose-dependency which correlated with decreased testes weights. This suggested a relationship to treatment with CDR132L. However, the focal or multifocal distribution of the tubular atrophy, as well as the absence of microscopic changes that may indicate a test item induced testicular toxicity, such as degenerate or apoptotic germ cells, multinucleated giant cells or an adaptive hyperplasia of Leydig cells, may also suggest that the findings are incidental. Due to the potential reversibility of the observed testes atrophy, the findings are regarded as non-adverse. Due to the absence of degenerative findings in the kidneys and lymph nodes, the minimally increased severity of potentially reversible testes findings, and the minimally increased

number and severity of accompanying findings in the epididymides at 20 mg/kg, the NOAEL was assigned to 20 mg/kg.

2.2.2 Overview of Clinical Studies

The FIH study explored 4 dose levels that ranged from CCI mg/kg. All doses were found to be safe and well tolerated. There were no deaths or serious adverse events (SAEs) during the study, and no TEAE led to treatment or study discontinuation. A total of 53 TEAEs were reported in 22 patients (78.6% of all) including placebo-treated patients. Of the 53 TEAEs, 4 were considered related to CDR132L. All TEAEs were mild in severity and all resolved. According to adverse reaction rules, no safety limits were exceeded across all cohorts of the study. The most common CDR132L-related TEAE was dizziness, with 2 patients reporting 1 event each. The frequency of TEAEs did not increase with dose escalation, so that no dose-response relationship was demonstrated. The TEAEs reported were consistent with the underlying patient population and their concomitant medication. There were no adverse events of special interest (AESIs) (i.e., thrombocytopenia) and even though there was 1 episode of paravasal infusion, no injection site reactions have been recorded in this study. No telemetry, Holter ECG, or ECG parameter (blood pressure [BP] and heart rate) were considered to represent clinically significant changes from baseline at the time of recording by the reviewing cardiologist. There were no notable, treatment-related, or clinically significant changes in liver function, renal function, or other laboratory results (N-terminal pro B-type natriuretic peptide [NT-proBNP] or high-sensitivity cardiac troponin [hs-cTn]), vital signs (BP and heart rate), or physical examinations from baseline in any CDR132L group or placebo. CCI

This proof-of-concept Phase 2 study will evaluate the efficacy of CDR132L in improving cardiac function and safety in patients with reduced left ventricular ejection fraction (LVEF) for 12 months post MI. Though safety has been proven in the pre-clinical studies and in a FIH study, the safety needs to be confirmed in a larger cohort of patients, which will be further assessed in this study.

2.3 Benefit/Risk Assessment

Heart failure is a serious condition with high mortality and frequent episodes of worsening that often requires hospitalization or emergency department (ED) care. CDR132L offers a novel therapeutic option in HF, by reversing the adverse cardiac remodeling and improving cardiac function. CDR132L is a synthetic and chemically modified ASO that selectively inhibits miR-132. A considerable number of ASOs containing identical or similar chemical modifications have been tested in clinical studies and some ASOs have been approved as medicinal products in the European Union (EU) and the United States (US), e.g., Spinraza (nusinersen), Tegsedi (inotersen).

Miravirsen, another PS-LNA modified ASO targeting the liver expressed miRNA-122 is currently in Phase 2 clinical study for treatment of Hepatitis C virus infection.¹⁸

The favorable PK, safety, tolerability, dose-dependent PK/PD relationship and high clinical potential for CDR132L has been demonstrated in vitro as well as in vivo in CCI and in a highly clinically relevant CCI model of HF. No potential CNS effects of CDR132L were reported in a 4-week toxicity study in CCI. The potential cardiovascular (CV) effects were determined by telemetry in minipigs and demonstrated no deaths, no signs of local intolerance at infusion sites, and no signs of systemic toxicity at any dose level. Additionally, no influence was noted on physical activity, BP, heart rate, or ECG parameters. Similarly, exposure of CDR132L in CCI had no demonstrable adverse effects on lung function parameters. The FIH study explored 4 dose levels that ranged from CCI mg/kg. All doses were found to be safe and well tolerated. There were no deaths or SAEs during the study, and no TEAE led to treatment or study discontinuation.

Potential adverse effects of CDR132L may relate to “on-target” (sequence-specific miR-132 inhibition) and “off-target” (sequence unspecific, class-effects of chemically modified oligonucleotides) effects. The safety profile of CDR132L has been evaluated in GLP-compliant safety pharmacology and repeat-dose toxicity studies using up to 9 IV applications of CDR132L given each 4 weeks apart, which covered a significantly longer exposure, than the 3 administrations planned in this Phase 2 study. There is clinical information from only 1 FIH study to predict adverse effects beyond those observed in safety pharmacology and toxicity studies. However, there is comprehensive clinical experience with other locked nucleic acid-phosphorothioate oligonucleotides and these data suggest a low risk of class-specific side effects and/or off-target effects with these types of compounds. Since adverse effects on the liver and kidneys may be anticipated from findings in the repeat-dose toxicity study at high dose tested (60 mg/kg), liver and kidney values will be closely monitored during the clinical study.

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More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of CDR132L may be found in the Investigator’s Brochure (IB).⁸

3.0 OBJECTIVES AND ENDPOINTS

This is a Phase 2, multicenter, randomized, parallel, 3-arm, placebo-controlled study to assess the efficacy and safety of CDR132L in patients with reduced LVEF ($\leq 45\%$) after MI. The objectives and endpoints are outlined in [Table 2](#).

Table 2 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To assess the efficacy of 2 dose levels (5 and 10 mg/kg) of CDR132L compared with placebo administered in 3 single IV doses given 28-days apart in patients with reduced LVEF $\leq 45\%$ after MI (STEMI or NSTEMI) as add-on therapy to SoC treatment 	<ul style="list-style-type: none"> Percent change from baseline in LVESVI (screening to occur at least 3 days after MI diagnosis as measured by ECHO [central laboratory]) at Month 6
Secondary	
<ul style="list-style-type: none"> To assess the safety of 2 dose levels (5 and 10 mg/kg) of CDR132L compared with placebo 	<ul style="list-style-type: none"> Frequency of adverse events and abnormalities in clinical laboratory assessments, vital signs, physical examination, ECGs, and urinalysis
<ul style="list-style-type: none"> To assess the effects of CDR132L compared with placebo on cardiac function 	<ul style="list-style-type: none"> Change from baseline LVEF (absolute/relative) at Months 3, 6, and 12 Change from baseline LVESVI at Month 3 (absolute/relative), Month 6 (absolute), and Month 12 (absolute/relative)
<ul style="list-style-type: none"> To assess the effects of CDR132L compared with placebo on efficacy-related biomarkers 	<ul style="list-style-type: none"> Change from baseline in absolute/relative troponin T (ng/L) at Months 3, 6, and 12 Change from baseline in absolute/relative values over time for the following efficacy-related biomarkers: <ul style="list-style-type: none"> N-terminal pro B-type natriuretic peptide (NT-proBNP)
<ul style="list-style-type: none"> To assess the effects of CDR132L compared with placebo on patient well-being 	<ul style="list-style-type: none"> Well-being as evaluated by change from baseline at Months 6 and 12 in the following parameters: <ul style="list-style-type: none"> Mean KCCQ score and mean scores of subdomains (symptom burden, physical limitation, and quality of life)
Exploratory	
<ul style="list-style-type: none"> CCI [REDACTED] 	<ul style="list-style-type: none"> CCI [REDACTED]
<ul style="list-style-type: none"> CCI [REDACTED] 	<ul style="list-style-type: none"> CCI [REDACTED]

Objectives	Endpoints
	<div><div></div><div></div><div></div></div>
<div><div></div></div>	<div><div></div></div>

Abbreviations: ECG = electrocardiogram; ECHO = echocardiography; HF = heart failure; IV = intravenously; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; MI = myocardial infarction; CCI = CCI; NSTEMI = non-ST-segment elevation myocardial infarction; NYHA = New York Heart Association; SoC = Standard of Care; STEMI = ST-segment elevation myocardial infarction.

4.0 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, multicenter, randomized, parallel, 3-arm, placebo-controlled study to assess efficacy and safety of CDR132L in patients with reduced LVEF ($\leq 45\%$) after MI. As shown in [Figure 1](#), this study consists of a Screening Period (to occur at least 3 days after MI diagnosis), a 6-month Double-blind Period, and a 6-month Prolonged Follow-up Period with the End of Study (EOS) Visit at Day 360/Month 12.

Patients will be screened to determine eligibility at least 3 days after MI diagnosis; all eligibility criteria must be confirmed no later than 14 days after MI diagnosis. Screening and dosing can be done in an inpatient (in case patients are hospitalized due to MI or HF) or outpatient setting. A total of approximately 280 unique individual patients will be randomly assigned to the 3 treatment groups in 1:1:1 ratio, with approximately 90 patients in each treatment group. Groups 1 and 2 will include patients who will receive CDR132L 5 mg/kg or 10 mg/kg, respectively. Patients in the placebo group (Group 3) are included for evaluation of efficacy and safety.

On Day 1 (preferably within one day after randomization but no later than 4 days after randomization), patients will receive CDR132L 5 mg/kg, CDR132L 10 mg/kg, or placebo IV. The second IV dose of the patient's assigned treatment will be administered on Day 29 ± 2 days, and the third IV dose on Day 57 ± 2 days. For doses administered in an outpatient setting, the patient should be observed for at least 30 minutes after dosing.

All patients will be required to attend the study visits as described in the Schedule of Activities (SoA; [Section 1.3](#)). All patients will receive SoC therapy post MI and eventually for HF. CDR132L or placebo will be administered as add-on therapy to the SoC treatment. All patients will be followed for 10 months for efficacy and safety assessments. Overall, study duration for each patient will be approximately 12 months.

A Data Safety Monitoring Board (DSMB) will closely supervise all data to monitor the safety of all patients. The DSMB Charter will describe the membership, roles, responsibilities, and operating guidelines of the DSMB.

Approximately 70 study sites will be selected according to their expertise in performing complex, early phase clinical studies as well as their ability to follow guidelines on established SoC treatment of post MI and HF patients. The study sites must have sufficiently trained study personnel to guarantee adherence to this study protocol.

4.2 Scientific Rationale for Study Design

This study will assess the efficacy and safety of CDR132L in patients with reduced LVEF ($\leq 45\%$) after MI (index event). Patients will be administered either 5 mg/kg or 10 mg/kg of CDR132L or placebo on Days 1, 29 ± 2 days, and 57 ± 2 days. Patients who will receive placebo will constitute

the control group that will help to determine which effects will pertain to the study drug (CDR132L) and which will not. Patients in this study will be assigned to a treatment regimen according to a randomization schedule and will enter the Double-blind Period whereby patients and clinical study site staff will be blinded to the active or placebo study treatment. CDR132L and placebo will be identical in appearance. In this study, patients who are prematurely discontinued will still be followed further for efficacy and safety assessments.

4.2.1 Rationale for Patient Selection

Due to its unique MoA, the main effect of CDR132L is to halt and reverse pathological cardiac ventricular remodeling. Adverse remodeling is the hallmark of post MI HF development irrespective of the clinical presentation of MI. In clinical practice, a combination of criteria is required to meet the diagnosis of acute myocardial infarction (AMI), which includes the detection of an increase of the cardiac biomarker troponin (preferably hs-cTn) T or I, and at least one of the following:²¹

- Symptoms of myocardial ischemia.
- New ischemic ECG changes.
- Development of pathological Q waves on ECG.
- Imaging evidence of loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.

Based on ECG evaluation, most patients will ultimately develop ST-segment elevation myocardial infarction (STEMI), but some patients will exhibit acute chest discomfort without persistent ST-segment elevation (non-ST-segment elevation myocardial infarction [NSTEMI]; including transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves, or pseudo-normalization of T waves; or the ECG may be normal).

The proportion of patients with NSTEMI increased from approximately 30% in 1995 to approximately > 50% in 2015, mainly accounted for by a refinement in the operational diagnosis of NSTEMI.²²

For both STEMI and NSTEMI patients, the pathological correlate at the myocardial level is cardiomyocyte necrosis in the infarcted area as indicated by the increase in hs-cTn T or I levels. The ensuing changes after tissue necrosis involve complex interactions in the myocardium between the cellular and extracellular components, under neurohormonal regulation. Due to increased load on the non-infarcted myocardium, the process of cardiac remodeling including pathological growth, impaired contractility, and increases in cardiac fibrosis is initiated.

We have shown that miR-132 induces all aforementioned hallmarks of cardiac remodeling. More importantly, this goes in hand with increased cardiac and plasma miR-132 levels in patients with various forms of HF. Finally, cardiac remodeling processes lead to progressive left ventricle (LV) dilatation (measured by increased LV end-systolic and end-diastolic volumes).

In ischemic as well as non-ischemic HF models, the beneficial anti-remodeling effects of CDR132L treatment are postulated to be attributed to its anti-hypertrophic, pro-contractile, and anti-fibrotic effects. The miR-132, which is the direct target of CDR132L, is a central switch in the molecular mechanism of HF progression as evidenced by genetic and pharmacological animal data. CDR132L blocks aberrant cardiac miR-132 levels, and thereby:

- normalizes aberrant functional miR-132 levels in the myocardium,¹⁻³
- normalizes calcium signaling and contractility,^{2,3}
- reduces pro-hypertrophic nuclear factor of activated T cells (NFAT) signaling leading to lower B-type natriuretic peptide levels,¹⁻⁴ and
- attenuates maladaptive cardiac remodeling by additional anti-fibrotic effects.¹⁻⁴

The results in relevant pre-clinical studies in post MI HF provide clear evidence that CDR132L treatment provides persistent and clinically relevant therapeutic effects on cardiac function in both STEMI and NSTEMI patients given that:

- acute ischemia is not the only trigger for increased cardiac miR-132 expression and
- the anti-remodeling MoA of CDR132L is expected to positively benefit both ischemic and non-ischemic HF conditions (as outlined above).

In summary, due to CDR132L's specific MoA, both patients with either STEMI or NSTEMI will be included in this study.

4.3 Justification for Dose

4.3.1 Justification for Selection of Planned CDR132L Doses

Justification for the selected CDR132L doses (5 mg/kg and 10 mg/kg) in the present Phase 2 study considers the results from the following: non-clinical safety, tolerability, PK, and pharmacodynamic studies, the toxicology studies in CCI (see the IB⁸), as well as the Phase 1b study in otherwise healthy HF patients. The approach was further guided by an elaborate PK/PD modeling of the anticipated CDR132L exposures in humans. Based on the recommendation by the regulatory authority, Medicines Evaluation Board of the Netherlands, on the selection of an appropriate time window for the safety follow-up in the Phase 2 study, an additional PD modeling was performed to project the changes in the miR-132 target plasma levels over time in patient cohorts of the Phase 1b study beyond the study endpoint at Day 112. The aim of the clinical Phase 2 study dosing strategy is to demonstrate efficacy and successful target engagement.

Dose Selection

Since in the Phase 1b study, no dose-limiting toxicity was observed in human subjects up to a dose of 10 mg/kg in a once per month administration scheme, this dose was considered safe for the planned Phase 2 study (CDR132L-P2-01), which comprises the same administration regimen with regard to the dosing intervals.

Pre-clinical assessment of CDR132L in GLP-like studies such as early post MI (CDR132L-NC-03-PD)² and chronic post MI HF CCI model (CDR132L-NC-10-PD)³ including more than 180 CCI demonstrated clinically relevant improvement in cardiac function, thereby reversing pathological cardiac remodeling, inhibition of cardiac fibrosis, and pathological cardiomyocyte growth post MI. Simultaneously, CDR132L doses of 5 mg/kg and 10 mg/kg also improved systolic and diastolic function applying.

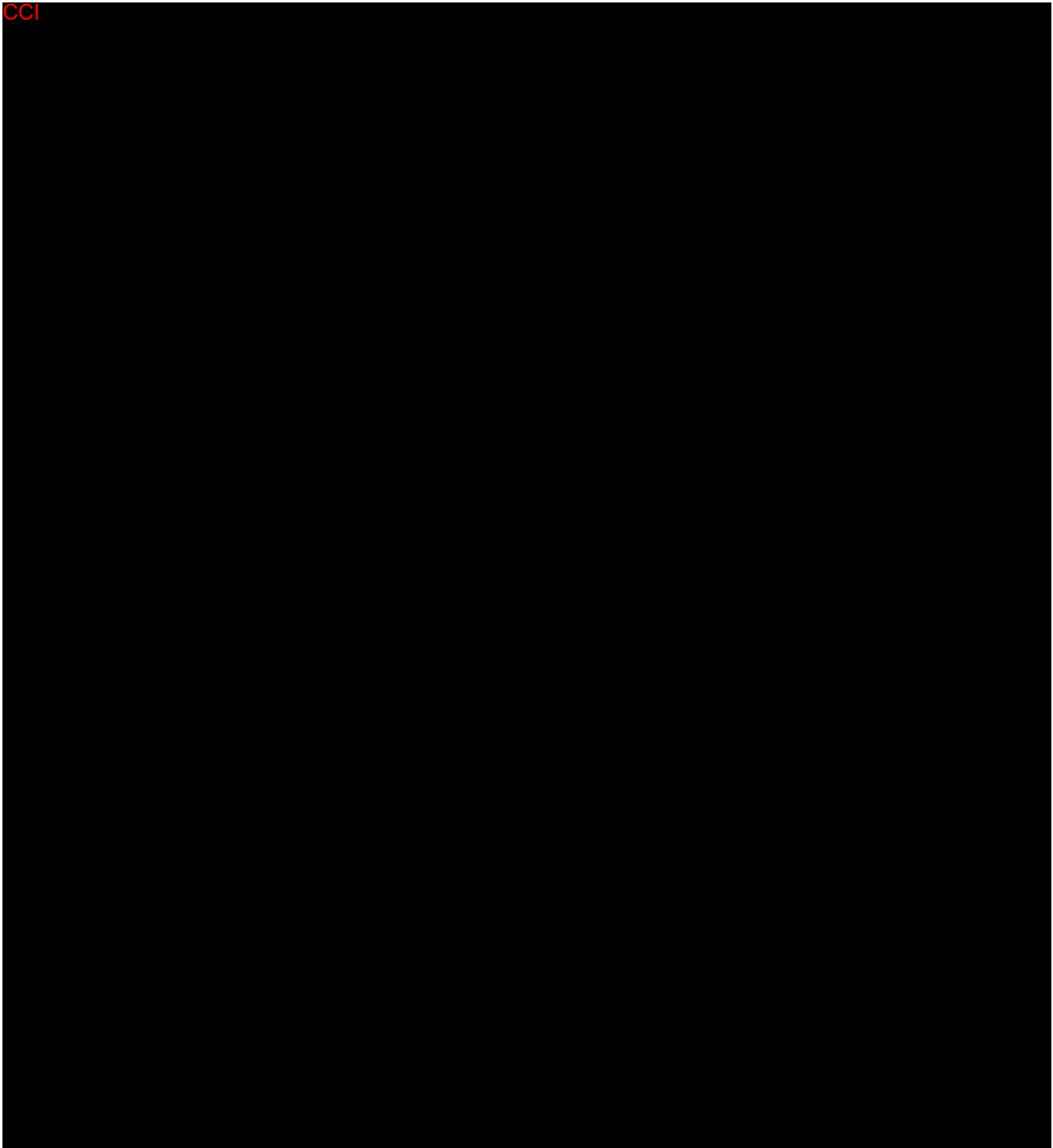
It was demonstrated that CDR132L tissue concentrations positively correlated with improvement of cardiac function, as measured by delta LVEF (change in LVEF between study endpoint and the day of first administration) in both early post MI and chronic HF CCI models. Additionally, CDR132L levels correlated with the reduction of functional tissue levels of its target gene, miR-132, in a linear manner. Importantly, CDR132L administrations reduced circulating miR-132 in plasma in early post MI (data available up to 6 months of treatment; CDR132L-NC-03-PD) and in chronic post MI HF pig model (CDR132L-NC-10-PD).

In addition, assessment of CDR132L CCI in humans, compared with the large animal CCI, confirmed a high level of inter-species translatability (see Figure 2). The CDR132L CCI profiles determined in humans and CCI show inter-species consistency with no signs for drug accumulation. CCI

CDR132L shows only a slightly prolonged initial half-life in human when considering a bi-phasic kinetic of the compound (1 h at CCI mg/kg to 2.49 h at 10 mg/kg).

Figure 2 CDR132L Pharmacokinetics in Human and Pig

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Although this modeling approach provided a reasonable dose range that fits to the results from the current set of data, the small sample size and level of variability of the Phase 1b study data had to be considered for mitigating the risk of administering an ineffective dose. From a mathematical point of view, the dose should not be chosen close to the lower limit of [REDACTED] mg/kg, but rather at the higher limit to consider the limitations in the data model adequately. Based on these CCI [REDACTED]

considerations, 5 mg/kg was selected as the low dose and by applying an additional margin factor of 2, 10 mg/kg was selected as the high dose in the present Phase 2 study, CDR132L-P2-01. Both doses would be adequately covered by the safety data, as CDR132L was well tolerated in the efficacy studies in CCI as well as in toxicological studies in CCI and CCI with monthly administrations for up to 9 months tested (CDR132L-NC-20-CRDT). Also, PD studies in the chronic post MI HF pig model, starting treatment was 1 month post MI, showed beneficial effects with 3 monthly doses and 5 monthly doses of 5 mg/kg with no safety signals.

Mean exposure in terms of area under the curve for CDR132L in patients of the high-dose group (10 mg/kg) in the clinical Phase 1b trial was approximately 397,000 ng*h/mL. This dose level and the associated systemic exposure were not associated with any safety or tolerability signals in patients. Due to the lack of accumulation in the Phase 1b study, it is anticipated that the highest dose of 10 mg/kg to be administered in the Phase 2 study will result in exposure levels that are comparable to those noted in the Phase 1b trial.

Thus, Cardior selected 3 single IV doses of CDR132L, 28 days apart (Day 1, Day 29, and Day 57) from each other to prolong the therapeutic effect by an additional month of CDR132L of cardiac tissue exposure.

Safety Follow-up Window

Regarding the selection of an appropriate time frame for the safety follow-up in the Phase 2 study, an additional PD modeling was performed to project the changes in the miR-132 target plasma levels for the months after the last CDR132L administration in the Phase 1b study. With CDR132L treatment achieving cardiac improvement, Cardior envisages to achieve a normalization of miR-132 levels on the long run. However, the Phase 1b data generated so far comprised data of 3 months after treatment, and the present Phase 2 study aims to provide data regarding miR-132 levels for a longer period of time, i.e., 10 months after the last dose of CDR132L.

In the Phase 1b study, miR-132 plasma assessments were only performed up to the endpoint of the study at Day 112 (3 months after the last CDR132L administration), wherein miR-132 plasma levels were still markedly reduced due to the sustained pharmacological activity of CDR132L. To ensure that the planned duration of safety follow-up in the planned Phase 2 study will be sufficient to cover the time span of CDR132L pharmacologic activity in the heart and other organs of the patients, a modeling of the miR-132 plasma levels was performed to project the time course of the return of miR-132 plasma levels to baseline.

Reduced miR-132 levels in plasma are due to the effect of CDR132L on plasma and tissue miR-132 as part of the MoA of CDR132L. The level of CDR132L in plasma remains very low but constant over time during the late part of the elimination phase, which is supported by the Phase 1b plasma CCI data, where the levels reached the lower limit of quantification after 48 hours. After CDR132L administration and the initial phase of distribution, the source of plasma CDR132L in the circulation is released from tissue, which is balanced by its elimination. Rebound of the miR-

132 level in plasma happens when plasma and tissue levels of CDR132L decrease over time, due to the depletion of CDR132L in tissues.

Based on these assumptions and the projection of the Phase 1b miR-132 study data, it is expected that miR-132 plasma levels after treatment with 10 mg/kg in humans will reach baseline levels approximately 6.5 months after the last dose.

As described above, the data from the Phase 1b study and the large CCI show a high level of comparability and translatability from CCI to humans. Thus, the CDR132L tissue exposure data from the CCI long-term study (CDR132L-NC-07-PK) was used to model the time course of CDR132L exposure in human heart and liver. When comparing the graphs of CDR132L elimination in heart and liver to the projections of miR-132 plasma level returning to baseline level in humans, the time course of both is highly similar. The increase of plasma miR-132 levels over time in the patients is moving along with the decreasing CDR132L concentrations, as shown in [Figure 3](#) below.

Based on this data, a 10-month follow-up after the last dosing is sufficient to provide an adequate time window for evaluating safety of CDR132L at the selected doses of 5 mg/kg and 10 mg/kg.

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4.3.2 Timing of Dose for Each Patient

Patients will receive a single IV infusion treatment for approximately 18 minutes of CDR132L 5 mg/kg, CDR132L 10 mg/kg, or placebo on Day 1, Day 29 ± 2 days, and Day 57 ± 2 days, according to the randomization list.

4.4 End of Study Definition

A patient is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of the last patient in the study or last scheduled procedure shown in the SoA for the last patient in the study globally.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

1. Male or female of non-childbearing potential patients, aged ≥ 30 to ≤ 80 years at the date of signing informed consent which is defined as the beginning of the Screening Period.
2. Spontaneous AMI (type I) based on the universal MI definition with randomization to occur no later than 14 days after index event diagnosis.²³
3. Patient with a LVEF $\leq 45\%$ as measured by ECHO after MI diagnosis (STEMI or NSTEMI).
4. Patient with NSTEMI with evidence of significant myocardial necrosis, evidenced through a troponin T or troponin I increase to at least 5 times the upper limit of normal (ULN) at MI index event diagnosis.
5. Patient with previous MI events in history can be included.
6. A male patient must agree to use contraception as detailed in [Appendix 5](#) of this protocol during the treatment period and for at least 30 days after the last dose of study treatment and refrain from donating sperm during this period.
7. Patient with body weight of ≤ 120 kg.
8. N-terminal pro B-type natriuretic peptide level ≥ 125 pg/mL and < 8000 pg/mL.
Note: NT-proBNP values required for eligibility confirmation may be collected at any time post MI either through medical history (e.g., site has collected it as SoC once the patient came to the hospital), through a local laboratory assessment, or by sending a sample to the central laboratory.
9. Patient with STEMI/NSTEMI who underwent percutaneous coronary intervention or angiography (if no indication for stent placement or balloon procedure) for this event.
10. Capable of giving signed informed consent as described in [Appendix 2](#), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. A woman of childbearing potential (WOCBP) as defined in [Appendix 5](#).
2. Patient with HF of non-ischemic origin; e.g., myocarditis, alcoholic cardiomyopathy.
3. Patient with history of decompensated HF or a history of LVEF $< 30\%$ within 6 months prior to MI index event.
4. Patient with NYHA class IV at screening or randomization.

5. Patient has any planned cardiac intervention (, angiogram without angioplasty is acceptable) or any other planned surgery after the Screening Period.
6. Patient has severe valvular heart disease.
7. Patient has systolic BP < 90 mmHg or > 180 mmHg, diastolic BP < 50 mmHg or > 110 mmHg, and/or heart rate < 50 or > 100 beats/minute at screening or randomization.
8. Patient with an estimated glomerular filtration rate < 30 mL/min/1.73 m² or on dialysis.
9. Patient with hepatic insufficiency classified as Child-Pugh B or C.
10. Patient with known active human immunodeficiency virus, Hepatitis B, or Hepatitis C infection at screening.
11. Impaired hepatic function defined by a total bilirubin level of $\geq 2 \times$ the ULN and ALT levels of $\geq 3 \times$ ULN.
12. Patient has medical history of disease(s) affecting the blood-brain-barrier, e.g., stroke within 6 months or multiple sclerosis.
13. Patient has medical history of bleeding disorders or has thrombocytopenia (platelets < 100,000/ μ L).
14. Patient has poorly controlled diabetes as determined by the Investigator.
15. Patient is currently on treatment for epilepsy.
16. Patient has a current or relevant history of physical or psychiatric illness that is/are not stable or may require a change in treatment, use of prohibited therapies during the study, or cause the patient to be unlikely to fully comply with the requirements of the study or complete the study, or any condition that presents undue risk from the study drug or study procedures.
17. Patient has a history or presence of any of the following cardiac conditions: known structural cardiac abnormalities beyond HF, family history of long QT syndrome, cardiac syncope, or recurrent, idiopathic syncope.
18. Any clinically significant abnormalities, at the discretion of the Investigator, in rhythm, conduction, or morphology of resting ECG that pose an additional safety risk to patients. This will include patients with any of the following (at Screening Visit or Day -1):
 - a) Clinically significant PR (PQ) interval prolongation.
 - b) Intermittent second- or third-degree atrioventricular block.
 - c) Sustained cardiac arrhythmia including (but not limited to) supraventricular tachycardia, any symptomatic arrhythmia with the exception of isolated extra systoles.
19. Patient with active and clinical-relevant “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)” infection confirmed as per the local testing guidelines at screening.
20. Patient has other significant disease or disorder which, in the opinion of the Investigator, may put the patient at risk because of participation in the study or may influence the result of the study or the patient's ability to participate in the study.
21. Patient has received an investigational product or treated with an investigational device within 90 days prior to first study drug administration.
22. Patient has known or suspected intolerance or hypersensitivity to the study drug, any closely related compound, or any of the stated ingredients.

23. Patient is not to be enrolled into the study if they received any prohibited therapy within 3 months before the first administration of study drug (please see also section 6.5.1):
- a) Treatment with anticancer therapy (chemotherapy, immunotherapy, radiotherapy, targeted therapy, or gene therapy) .
 - b) Administration of any other investigational agent.
24. Patient is involved in the planning and/or conduct of the study (applies to Sponsor staff, staff at the study site, and third-party vendors).

5.3 Lifestyle Recommendations

As part of SoC, lifestyle considerations are important, and implementing healthy behaviors (e.g., smoking cessation, physical activity, healthy diet, and maintaining a healthy weight) significantly decreases the risk of future CV events. Investigators should advise patients to adapt their lifestyle according to locally applicable recommendations for HF patients.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Patients who do not meet the criteria for participation in this study may be rescreened once. Rescreened patients should not be assigned the same patient number as for the initial screening.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a patient according to the study protocol.

6.1 Study Treatment(s) Administered

CDR132L or placebo will be administered IV as detailed in Table 3. The Pharmacy Manual contains detailed information regarding the storage, preparation, destruction, and administration of each treatment. The pharmacy staff preparing the study drug will not be blinded to study drug assignment.

The body weight assessed at the last visit prior to dosing or on the same day should serve as the reference weight for dose calculation.

Table 3 Study Treatment Details

Study Treatment Name:	CDR132L	Placebo
Dosage Formulation:	CCI [REDACTED]	Commercial sterile 0.9% NaCl (saline) solution will be used as formulation for placebo control.
Unit Dose Strength(s)/Dosage Level(s):	CDR132L 5 mg/kg, 10 mg/kg	Sterile 0.9% NaCl (saline) solution
Route of Administration:	Intravenous infusion	Intravenous infusion
Flow Rate (Details will be provided in the Pharmacy Manual)	CCI [REDACTED]	CCI [REDACTED]
Packaging and Labeling:	Study drug will be provided in a vial and will be labeled as per country requirement. Labeling of study treatment is performed by BAG Health Care GmbH, Amtsgerichtsstr. 1-5, 35423 Lich, Germany.	Locally-approved commercially available sterile 0.9% NaCl (saline) solution will be used.
Manufacturer:	Drug Substance: Biospring GmbH, 60386 Frankfurt, Germany. Drug Product: BAG Health Care GmbH, Amtsgerichtsstr. 1-5, 35423 Lich, Germany.	Locally-approved commercially available sterile 0.9% NaCl (saline) solution will be used.

6.2 Preparation/Handling/Storage/Accountability

The study drug will be supplied by the Sponsor (or designee), along with the batch/lot numbers and Certificates of Analysis. As reconstitution and dilution solvent for preparation of the CDR132L dosing solutions, and for preparation of the placebo dosing solution, commercially available, locally-approved sterile 0.9% NaCl (saline) solution will be used, which will be sourced locally by the study site.

CDR132L study drug is stored at the recommended storage temperature of $-20 \pm 5^{\circ}\text{C}$ or $5 \pm 3^{\circ}\text{C}$. Based on stability studies, the current shelf-life of CDR132L vials is 36 months.

The pharmacy personnel must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

Detailed information regarding the preparation of IMP is provided in the pharmacy manual.

Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

The Investigator, a member of the study site staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

All patients will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS/IXRS). Before the study is initiated, the telephone number and call-in directions for the IWRS and/or the log in information and directions for the IWRS will be provided to each site.

This study drug will be administered in a double-blind fashion whereby patients and clinical study site staff will be blinded to the study treatment until all patients have completed Month 6, with study personnel having limited access to the randomization code. The investigational treatment and placebo will be masked since there are differences in their physical appearance. The assignment of treatment each patient will receive will not be disclosed to the Investigator, study site staff, patient, Sponsor, or study vendors. During the study, the individual randomization codes

will be kept in the site's clinical study pharmacy, accessible to the pharmacy personnel only. Sponsor staff involved in clinical decision-making (such as those involved in DSMB decisions) will be blinded to study drug assignment until all patients have completed Month 6.

Patients will be randomly assigned in a 1:1:1 ratio to receive study treatment. Study treatment will be administered at the study visits summarized in the SoA ([Section 1.3](#)). Investigators and patients will remain blinded to each patient's assigned study treatment until all patients have completed Month 6. In order to maintain this blind, an otherwise uninvolved 3rd party (i.e., pharmacy staff) will be responsible for the reconstitution and dispensation of all study treatment and will endeavor to ensure that there are no differences in time taken to dispense following randomization. The pharmacy staff preparing the study drug will not be blinded to study drug assignment.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study treatment records at the study site(s) to verify that randomization/dispensing has been done accurately.

Upon all patients completing of Month 6, after the database lock and after the blind is revealed, the randomization list will be filed in the Trial Master File.

6.3.1 Emergency Unblinding

Investigators at sites may unblind the treatment allocation for an individual patient if deemed necessary for medical reasons. In the event of such an emergency unblinding, the unblinded pharmacy staff, who have access to the treatment allocation through allocation from the IWRS system, can provide the treatment allocation for the requested individual patient to the Investigator. Unblinded site staff may utilize the IWRS to determine the treatment allocation. Additionally, the study drug preparation records present at the site pharmacy can be utilized to provide the treatment allocation to the Investigator and unblinded site staff will be required to cross-check these with the IWRS treatment allocation. In the event of an emergency unblinding, the site staff is required to report the event, including a rationale for the unblinding, through the IWRS and the patient's source notes.

6.4 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any changes from the intended regimen must be recorded in the electronic case report forms (eCRFs).

Doses of CDR132L or placebo will be administered by IV infusion by the Investigator or designee. Detailed instructions for dose administration will be included in the Pharmacy Manual.

Each dose of study drug will be administered by study personnel at each site and therefore treatment compliance will not be formally evaluated in this study. Each patient will be considered to have received a complete dose of study drug if they receive at least 80% of study drug per infusion.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving from 30 days prior to the Screening Period, at the time of enrollment, and receives during the study must be recorded on the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.
- For vaccines (if applicable): include brand name and manufacturer (plus lot number if available).

Medications/treatments for diabetes, atrial fibrillation, and HF according to SoC as per the latest local guidelines should be given during the study if patients are stable on therapy.

Patients using stable doses of prescription or over-the-counter medications for stable conditions may be enrolled at the discretion of the Investigator. During the study, other prescription or over-the-counter medications may be permitted at the discretion of the Investigator. In any case, the Investigator will inform the Sponsor about the concurrent medication given. Other investigational procedures and products while participating in this study are prohibited.

Details of all other prior and concomitant medications will be recorded by the Investigator on the eCRF and source record.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Prohibited Therapies

The following therapies are not permitted at any time before the patient's completion of the study:

- Treatment with anticancer therapy (chemotherapy, immunotherapy, radiotherapy, targeted therapy, or gene therapy).
- Administration of any other investigational agent .
- Vaccination with live vaccines. Of note: Administration of inactivated vaccines and mRNA vaccines is allowed (e.g., inactivated influenza vaccines or SARS-CoV-2 vaccines).

If administration of any prohibited therapy becomes necessary during the study for medical reasons, the patient must be discontinued from the study. The requirements for handling early discontinuations from study drug are described in [Section 7.0](#).

6.6 Dose Modification

Dose modifications will not be allowed. If a dose modification is needed, the patient should be discontinued from treatment and all end of treatment assessments completed.

6.7 Treatment After the End of the Study

The Sponsor will not provide any additional care to patients after they leave the study because such care should not differ from what is normally expected for patients with MI.

7.0 DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

A patient's study treatment should be discontinued for any of the following reasons:

Adverse event: A patient should be discontinued from the study if, in the judgment of the Investigator, the patient develops an AE such as an intercurrent illness or complication that is not consistent with the protocol requirements or that, in any way, justifies withdrawal from the study:

Liver function: One of the conditions outlined below following repeated testing (see [Section 8.3.4](#)) or if the Investigator believes that it is in best interest of the patient:

- $ALT > 8 \times ULN$.
- $ALT > 5 \times ULN$ for > 2 weeks.
- $ALT > 3 \times ULN$ and (total bilirubin $> 2 \times ULN$ or international normalized $> 1.5 \times ULN$).
- $ALT > 3 \times ULN$ with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$).

ECG: If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the Investigator or qualified designee will determine if the patient can continue in the study and if any change in patient management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding will be reported as an AE.

A patient who meets either below criterion based on ECG readings will be withdrawn from the study:

- $QTcF > 500$ msec OR uncorrected QT > 600 msec
- Change from baseline of $QTcF > 60$ msec

For patients with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTcF with Bundle Branch Block	Discontinuation QTcF Threshold with Bundle Branch Block
< 450 msec	> 500 msec
450 to 480 msec	≥ 530 msec

Renal function: clinically significant reduction in kidney function defined by a new requirement for renal dialysis, or two consecutive eGFR values of less than 27 ml/min/1.73 m².

Hypersensitivity: Patient has or develops hypersensitivity to CDR132L or one of the formula excipients.

Other, non-AE:

- Noncompliance with study protocol requirements.
- Investigator decision.
- Discontinuation of treatment on account of protocol deviation.
- Withdrawal by patient (see [Section 7.2](#)).
- Study termination by Sponsor or regulatory bodies/agency.

If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient must be discontinued from study treatment and the Sponsor or Sponsor designee must be contacted. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the patient to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor or Sponsor designee to allow the patient to continue in the study.

Patients who discontinue treatment will be followed up as patients who do not discontinue treatment unless consent is withdrawn. If applicable, Patients who discontinue treatment will be asked to attend visits 33±7 days, 93±7 days and 273±7 days after last dose. Data from those visits will be entered as V5, V6 and EoS, respectively.

The reason for discontinuation of study treatment will be recorded in the clinical records and the patient's eCRF.

Patients who discontinue study treatment will not be replaced.

See the SoA ([Section 1.3](#)) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.2 Patient Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3 Lost to Follow-up

Discontinuation of specific study sites or of the study are handled as part of [Appendix 2](#).

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.4 Criteria for Stopping the Study

The study can be terminated by the Sponsor at any time for any reason. Reasons for discontinuation may include, but are not limited to, any of the following:

- Reasons related to the benefit/risk assessment of participating in the study.
- Safety concerns that preclude continuation of the study.
- Regulatory reasons (e.g., an order from a regulatory authority to discontinue the study).
- Practical reasons (e.g., insufficient enrollment).
- Issues with the manufacture and/or supply of study drug.
- Business or financial factors that preclude continuation of the study.

Should this be necessary, patients must be seen as soon as possible and treated as a prematurely withdrawn patient. The Investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The Investigator will be responsible for informing the IRB/EC of the early termination of the study if applicable.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA ([Section 1.3](#)).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed 450 mL (in 12 weeks). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Patients should abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 3 hours before the clinic visit.

Patients should abstain from alcohol for 24 hours before the clinic visit.

8.1 Medical History

A medical history, including cardiovascular and surgical history, history of allergies, and history of prior (within 30 days prior to screening) medication and vaccine treatment will be obtained by the Investigator or qualified designee. Events and diseases will be recorded for up to 6 months prior to screening.

COVID-19 infections and vaccinations will be recorded regardless of their time of occurrence until EoS. At screening, the following information regarding prior COVID-19 infection should be recorded:

- COVID-19 that does not require hospitalization (e.g., asymptomatic, mild, or moderate).
- COVID-19 that requires hospitalization (e.g., COVID-19 pneumonia).
- Long COVID or post COVID-19 condition.

- COVID-19 vaccination status.

8.2 Efficacy Assessments

Planned time points for all safety assessments are provided in the SoA ([Section 1.3](#)).

8.2.1 Echocardiography Central Laboratory

The ECHO results will be read and interpreted for the study purposes centrally as described below. The assessing ECHO Reviewer will be blinded to the study treatment assignments.

8.2.1.1 *Left Ventricular End-systolic Volume Index*

Left ventricular end-systolic volume index is considered one of the standard ECHO markers for assessing risks in ischemic HF. The evaluation of change in left ventricular end-systolic volume index (LVESVI) at Month 6 from its value at baseline is the primary efficacy endpoint of this study. The ECHO will be performed to assess LVESVI. Full details of this procedure will be provided in the Imaging Study Manual.

8.2.1.2 *Cardiac Function – Left Ventricular Ejection Fraction*

Left ventricular ejection fraction is an established method for evaluation of left ventricular systolic function. A 2D ECHO will be performed in the ECHO central laboratory by trained personnel to assess LVEF. Contrast ECHO may be an available option to enhance image quality. Full details of this procedure will be provided in the Imaging Study Manual.

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8.2.1.4 *Global Longitudinal Strain*

Global longitudinal strain imaging of the LV is a method for objectively assessing the global and regional functions of the LV of the heart. Left ventricular longitudinal systolic function will be analyzed by 2D ECHO.

8.2.2 Electrocardiograms

An 12-lead ECG will be obtained as outlined in the SoA (see [Section 1.3](#)) using an ECG machine that automatically calculates the heart rate and measures PR, QRS and QT intervals.

The QRS complex as prognostic marker for HF severity will be analyzed as well as the change of ECG interpretations.

8.2.3 Patient Well-being

Patient's well-being will be measured by Kansas City Cardiomyopathy Questionnaire (KCCQ) either on paper or digitally.

8.2.3.1 *Kansas City Cardiomyopathy Questionnaire*

The KCCQ is a 23-item, self-administered questionnaire developed to independently measure the patient's perception of their health status, which includes HF symptoms, impact on physical and social function, and how their HF impacts their quality of life within a 2-week recall period.

8.2.4 Efficacy-related Biomarkers

8.2.4.1 *Absolute Changes from Baseline in NT-proBNP*

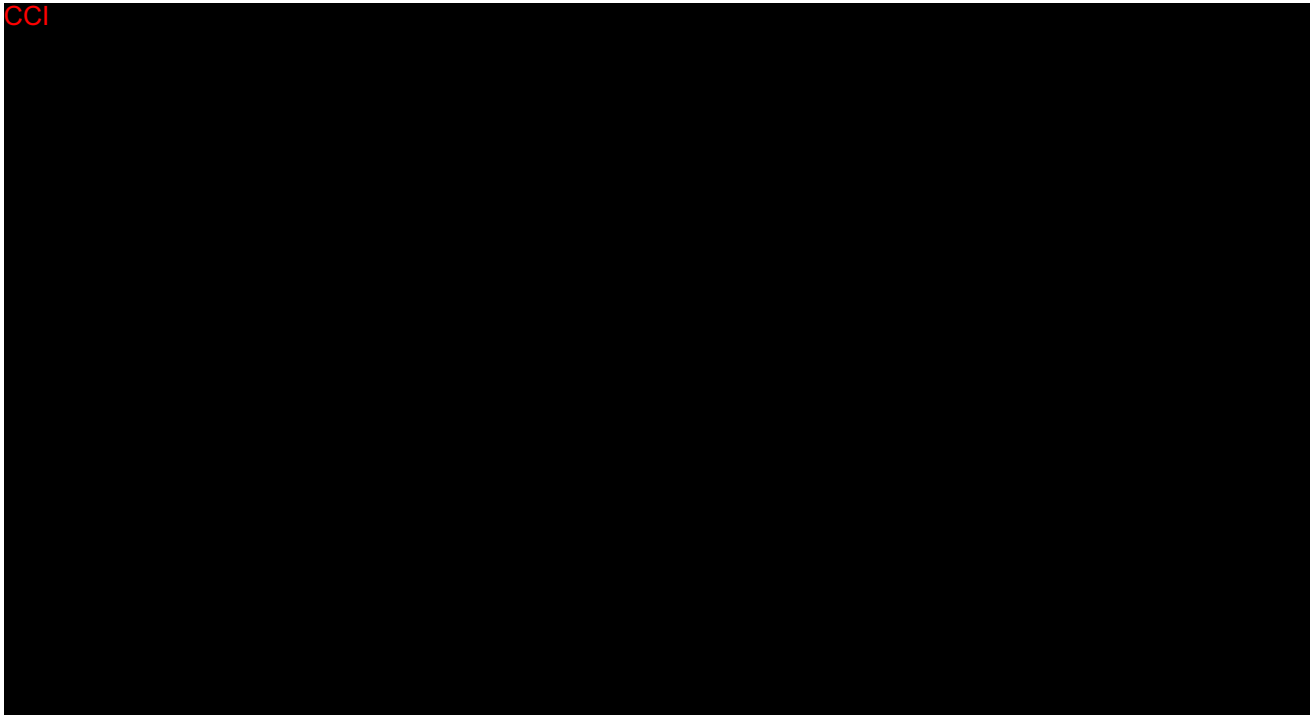
The increase in circulating NT-proBNP will reflect the diminished capacity of the heart to deliver oxygenated blood to the body. A test for NT-proBNP will be used to evaluate the severity of HF.

8.2.4.2 *Troponin T*

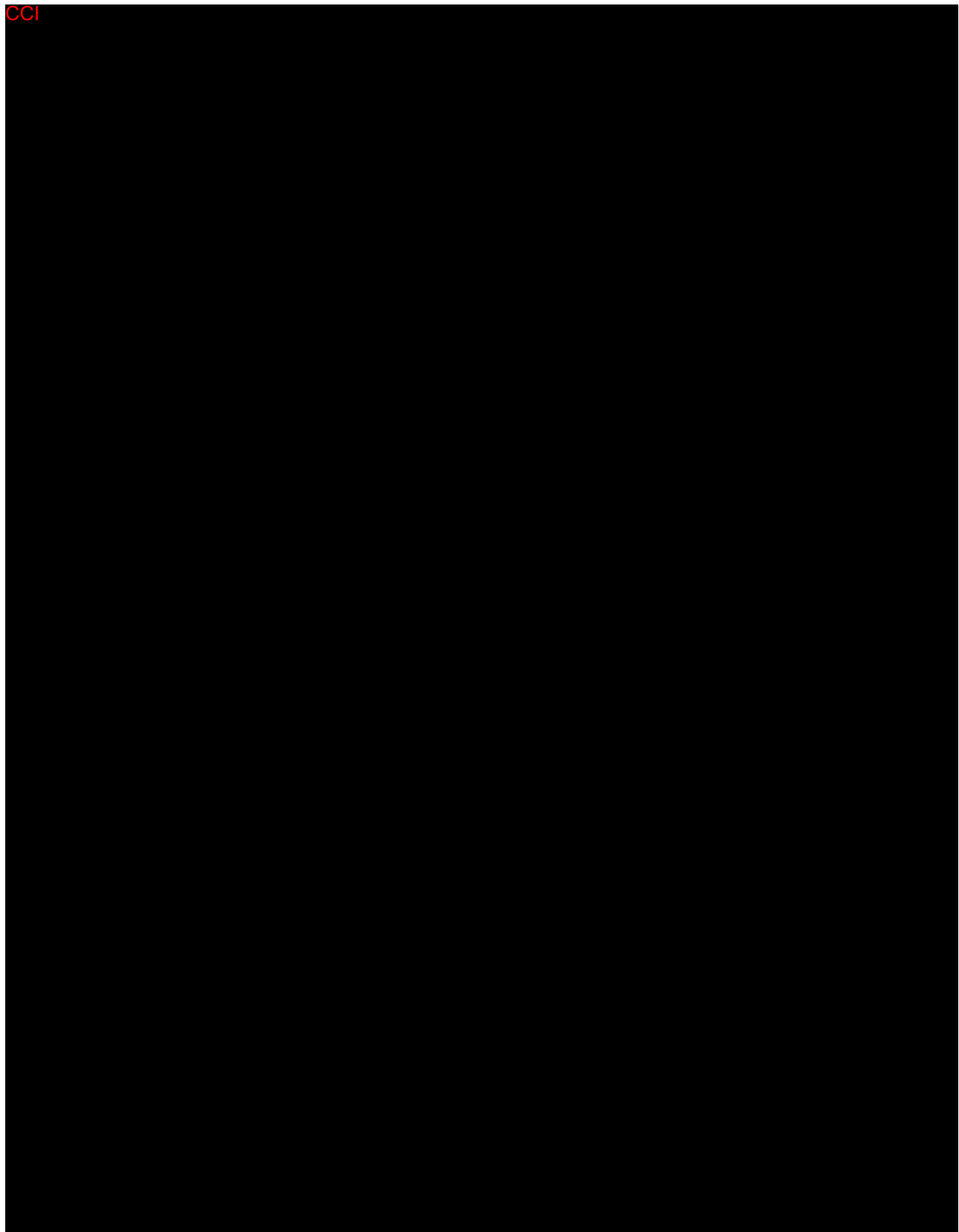
An elevated level of troponin T indicates heart muscle damage or HF and therefore troponin T is used as a biomarker of myocardial injury. Troponin T levels will be measured by hs-cTn.

8.2.5 Exploratory Assessments of Efficacy

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8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA ([Section 1.3](#)).

8.3.1 Physical Examinations

The Investigator or designee will perform a complete physical examination at screening. A brief physical examination will be conducted during the study unless a complete physical examination is needed.

A complete physical examination will include, at a minimum, assessments of the CV, Respiratory, Gastrointestinal, and Neurological systems. Height will only be measured at screening and weight will be measured and recorded per the SoA ([Section 1.3](#)).

A brief physical examination will include, at a minimum, assessments of the skin, lungs, CV system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

Body temperature, pulse rate, BP, and respiratory rate will be assessed.

Blood pressure and pulse measurements will be assessed in supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g., television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute). The average of the 3 BP readings will be recorded on the eCRF.

8.3.3 Electrocardiograms

12-lead ECG recordings should be made after the patient is rested in a supine position for at least 10 minutes. The postural changes by patients will be avoided during the ECG recordings and clinical staff will ensure that patients are awake during the ECG recording.

The frequency obtaining ECG values is outlined in the SoA (see [Section 1.3](#)) and the assessment will include heart rate and measures PR, QRS, and QT intervals will be automatically calculated upon entry into the eCRF.

Refer to [Section 7.0](#) for (QTcF) withdrawal criteria and any additional QTcF readings that may be necessary.

8.3.4 Clinical Safety Laboratory Assessments

See [Appendix 3](#) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within EOS should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor is notified.
- All protocol-required laboratory assessments, as defined in [Appendix 3](#), must be conducted in accordance with the laboratory manual and the SoA.
- The Investigator must determine whether an abnormal value in an individual study patient represents a clinically significant change from the patient's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as AEs.
- If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

For urinalysis, if deemed necessary, based on a clinically significant positive test, microscopic examination of urine will be performed. Microscopic examination result will supersede the urine dip result.

8.4 Adverse Events

The definitions of an AE or SAE can be found in [Appendix 4](#).

Adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the patient to discontinue the study treatment (see [Section 7.0](#)).

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs (non-serious and serious) will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA ([Section 1.3](#)).

However, medical occurrences related to the MI index event will be recorded on the Medical History/Current Medical Conditions section of the eCRF and not the AE section to avoid overreporting.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in [Appendix 4](#). The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of their awareness of the updated information.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor or designee.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in [Appendix 4](#).

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs, and non-serious AESIs (as defined in [Section 8.4.6](#)), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in [Section 7.3](#)). Further information on follow-up procedures is given in [Appendix 4](#).

8.4.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor or designee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met. See also [Section 8.4.1](#).

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/IEC, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy

Details of all pregnancies will be collected after the start of study treatment and until EOS.

If a pregnancy is reported, the Investigator should inform the Sponsor or designee within 24 hours of learning of the pregnancy and should follow the procedures outlined in [Appendix 5](#).

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.6 Adverse Events of Special Interest

An AESI is an AE of scientific or medical concern specific to the Sponsor or the particular product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. It may require further investigation to characterize and understand them. It could be serious or nonserious and may include events that may be potential precursors or prodromes for more serious medical conditions in susceptible individuals.

The AESI of thrombocytopenia will be reported by the Investigator as this has been reported for oligonucleotides but not so far for CDR132L.

8.5 Treatment of Overdose

An overdose is any dose of study treatment given to a patient that exceeds the dose described in the protocol. There is no information regarding overdose with CDR132L.

Any overdose, with or without associated AEs, must be promptly reported to the Sponsor or designee. In case of any AEs associated with the overdose, these should be reported on relevant AE/SAE sections in the eCRF.

8.6

CCI

CCI

8.7

CCI

CCI

8.8 Biomarkers

Biomarkers for efficacy and CCI efficacy analyses are provided in [Section 8.2.4](#) and [Section 8.2.5.4](#), respectively. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

All efficacy-related and CCI will be analyzed by a central laboratory. Additional details can be found in the Laboratory Manual.

8.9 Genetics

Genetics are not evaluated in this study.

8.10 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

This section summarizes the planned statistical analyses of the endpoints, including primary and secondary endpoints. The statistical analysis plan (SAP) will be developed and finalized before database lock for the 6-month primary efficacy and safety analyses and will describe the patient analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Any subsequent amendments to the SAP will be documented, with final amendments completed before unblinding of the data for the final analysis.

Primary analysis of efficacy and safety will be done once the last patient has completed the 6-month time point. Data from the Prolonged Follow-up Period will be analyzed separately once the last patient has completed last visit (Month 12). A clinical study report will be written following the completion of the study (Day 360/Month 12).

9.1 Sample Size Determination

The primary endpoint is defined as percent (%) change from baseline LVESVI at Month 6 compared with baseline (after reperfusion, before treatment start) on top of SoC as measured by ECHO (central laboratory).

For the sample size calculation, the two-sample t-test is used. The test level is set to 2.5% (one-sided). Assumptions are displayed below.

Left ventricular end-systolic volume index	Mean (change in %)	Standard deviation (%)
Placebo response	1	9
10 mg/kg	6	9
5 mg/kg	5	9
N = 90 per group	Step 1	96.0%
	Step 2	84.3%
	Overall	80.9%

Step 1 (10 mg/kg versus placebo):

A sample size of 90 in each group will have 96.0% power to detect a difference in means of 5 (the difference between a Group 1 mean, μ_1 , of 6 and a Group 2 mean, μ_2 , of 1) assuming that the common standard deviation is 9 using a 2-group t-test with a 2.5% one-sided significance level.

Step 2 (5 mg/kg versus placebo):

A sample size of 90 in each group will have 84.33% power to detect a difference in means of 4 (the difference between a Group 1 mean, μ_1 , of 5 and a Group 2 mean, μ_2 , of 1) assuming that the common standard deviation is 9 using a 2-group t-test with a 2.5% one-sided significance level.

Including 90 patients per group (270 total) will lead to a power of 96.0% for the first step (10 mg/kg vs placebo, difference in means of 5) and 84.3% for the second step (5 mg/kg vs placebo, difference in means of 4) of the hierarchical test procedure, resulting in an overall power of 80.9%. Ten additional patients should be included to compensate for early dropouts.

It is planned that approximately 280 patients will be enrolled/randomized into the study in a 1:1:1 ratio (approximately 90 patients each in 5 mg/kg, 10 mg/kg, and placebo groups). Assuming 10 patients will not be evaluable, it is anticipated that 270 patients will be evaluable (90 patients each in 5 mg/kg, 10 mg/kg, and placebo groups).

9.2 Populations for Analyses

For purposes of analysis, the analysis sets in [Table 4](#) are defined. Additional analysis sets may be defined in the SAP.

Table 4 Analysis Sets

Analysis Set	Description
Entered Analysis Set	All patients who sign the informed consent form.
Intent-to-treat	All patients in the Entered Analysis Set who are randomized to study drug. Patients will be analyzed according to their randomized study treatment.
Safety	All randomized patients who receive at least 1 dose of study drug (CDR132L or placebo) and have at least 1 post-dose safety assessment. Patients will be analyzed according to the treatment they actually received.

9.3 Statistical Analyses

9.3.1 Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, collection time, where available, will be compared with the first dose time to determine whether the measurement is pre-baseline or post-baseline. If time is not available, the measurement will be considered pre-baseline, but injection site reaction commencing on the reference start date will be considered post-baseline.

9.3.2 Efficacy Analyses

The Intent-to-treat (ITT) Population will be the primary analysis population. Additionally, sensitivity analysis will be done using the Full Analysis Set and will be described further in the SAP.

The estimand for establishing the efficacy of CDR132L consists of the mean difference in change from baseline in percent change in LVESVI at Month 6 among MI patients randomized to either active treatment or placebo group calculated in the ITT analysis set using analysis of covariance (ANCOVA). This primary analysis of the primary efficacy endpoint will be conducted regardless of intercurrent events, following the treatment policy strategy.²⁴ Under this strategy imputation of the primary efficacy endpoint among patient dropouts who are known to be alive during the assessment of the primary efficacy endpoint may be imputed. The efficacy of CDR132L based on mortality will be assessed at Month 12.

9.3.2.1 Primary Efficacy Analysis

The primary endpoint is defined as percent (%) change from baseline LVESVI at Month 6 compared with baseline (after reperfusion, before treatment start) on top of SoC as measured by ECHO (central laboratory).

The comparison will be done for the 10 mg/kg dose group versus placebo, followed by 5 mg/kg versus placebo within a hierarchical two-step test procedure.

The aim is to show superiority of the 10 mg/kg dose group (μ_{T10}) and the 5 mg/kg dose group (μ_{T5}) in comparison to placebo (μ_P) within a hierarchical test procedure with 2 steps:

Step 1

- H01: $\mu_{T10} \leq \mu_P$
- H11: $\mu_{T10} > \mu_P$

If Step 1 is successful, then proceed to Step 2.

If Step 1 is not successful, then do not proceed to Step 2.

Step 2

- H02: $\mu_{T5} \leq \mu_P$
- H12: $\mu_{T5} > \mu_P$

To show superiority, the effect of the 10 mg dose group on the percent change in LVESVI must be larger (i.e., higher decrease) than the effect within the placebo group.

The percent change from baseline in LVESVI will be analyzed using ANCOVA, with placebo acting as the reference. The model will include treatment as a fixed effect and baseline LVESVI as a covariate.

9.3.2.2 *Secondary Efficacy Analysis*

The change from baseline in continuous secondary endpoints will also be analyzed using ANCOVA, with placebo acting as the reference. The model will include treatment as a fixed effect and baseline value as a covariate.

9.3.2.3 CCI

CCI

9.3.3 Safety Analyses

Safety variables include incidence of AEs and TEAEs, laboratory test results, vital signs, ECG results, and physical examination findings. All safety analyses will be based on the Safety Population. No formal statistical analysis of the safety data will be performed.

Treatment-emergent adverse events are defined as AEs that first occurred or worsened in severity after the first administration of study treatment and prior to 30 days after the last administration of study treatment.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. For each study treatment, numbers of TEAEs and incidence rates will be tabulated by preferred term and system organ class (SOC). Treatment-emergent adverse events by maximum severity, TEAEs by relationship to study treatment, SAEs, TEAEs leading to death, and TEAEs leading to discontinuation of study treatment will be tabulated for each treatment group. Commonly occurring TEAEs, i.e., those that occur in 5% or more of the patients in either treatment group, will be summarized using descriptive statistics.

The AE summary tables will include counts of patients. Therefore, if a patient experiences more than one episode of a particular AE, the patient will be counted only once for that event. If a patient has more than one AE that is coded to the same preferred term, the patient will be counted only once for that preferred term. Similarly, if a patient has more than one AE within a SOC, the patient will be counted only once in that SOC.

All laboratory test results, vital signs measurements, ECG results, weight, and body mass index will be summarized for each treatment group using descriptive statistics at each visit for raw numbers and change from baseline. The incidence of treatment-emergent abnormal laboratory, vital sign, and ECG values will also be summarized using descriptive statistics.

Laboratory test variables will be summarized by treatment group and visit using descriptive statistics (number of patients, mean, standard deviation, minimum, maximum, and mean change

from baseline). Laboratory tests with categorical results (e.g., urinalysis) will be summarized by treatment group and visit by the number of patients in each category. Shift tables (low, normal, high) between baseline and post-baseline time points will be presented by laboratory test and treatment group. Laboratory tests with categorical results that cannot be analyzed by change from baseline or shift table analysis will not be included in these summaries but will be listed. Data obtained from laboratory tests not required by the protocol will not be summarized but will be listed.

Descriptive statistics of vital signs and ECG results at each visit will be presented by treatment group. Physical examination findings will be listed for each patient.

9.3.4 Missing Data

Sites will be instructed to minimize dropouts and if possible, collect to retrieve efficacy data among patients who withdraw from the study early. Such data from retrieved dropouts may be used to impute missing data.

Missing efficacy data (including those due to early discontinuations) may be imputed by having the previous visit value carried forward (last observation carried forward).

No safety data will be imputed.

9.4 Interim Analyses

No interim analysis for efficacy is planned. Primary analysis will be done once the last patient has completed the 6-month time point. Follow-up data after this time point will be analyzed separately once the last patient has completed last visit (Month 12). A clinical study report will be written following the completion of the study (Day 360/Month 12).

9.5 Data Safety Monitoring Board

A DSMB consisting of members who are independent from the Sponsor will be established. The DSMB membership will have a minimum of 3 members, including at least 1 specialist with expertise in Cardiology and an independent statistician, as appropriate. The DSMB is responsible for reviewing and evaluating unblinded safety data collected after the initiation of the study; however, the frequency could be adjusted based on accrual and pertinent dose information availability. The DSMB may also meet in ad hoc meetings at its discretion as needed in response to events occurring in the study. The DSMB will be responsible for making recommendations as to whether it is scientifically and ethically appropriate to continue enrollment, discontinue treatment groups, or stop the study. The detailed information on how to run or manage the DSMB will be described in the DSMB Charter.

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11.0 APPENDICES

Appendix 1**Abbreviations**

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
ANCOVA	Analysis of covariance
ASO	Antisense oligonucleotide
BP	Blood pressure
C _{max}	Maximum concentration
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CV	cardiovascular
DSMB	Data safety monitoring board
EC	Ethics Committee
ED	Emergency Department
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECHO	Echocardiography
EF	Ejection fraction
EOS	End of Study
EU	European Union
FIH	First-in-human
GCP	Good clinical practice
GDMT	Guideline-directed medical therapy
GLP	Good Laboratory Practice
HF	Heart failure
hs-cTn	high-sensitivity cardiac troponin
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

Abbreviation	Definition
IRB	Institutional review board
IV	Intravenous
IV(W)RS or IXRS	Interactive voice (web) response system
ITT	Intent-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVESVI	Left ventricular end-systolic volume index
MI	Myocardial infarction
CCI	
MoA	Mechanism of action
NOAEL	No-observed-adverse-effect-level
NSTEMI	Non-ST-segment elevation myocardial infarction
NT-proBNP	N-terminal pro B-type natriuretic peptide
CCI	CCI
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
QTcF	QT interval corrected using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SoA	Schedule of Activities
SoC	Standard of Care
SOC	System organ class
STEMI	ST-segment elevation myocardial infarction
T _{1/2}	half-life
US	United States
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative ([Appendix 6](#)). The study will not start at any study site at which the Investigator has not signed the protocol.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the patient and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the patient was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient.

Patients who are rescreened are required to sign a new ICF.

Data Protection

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the EU database a summary of the results

of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

All patient data relating to the study will be recorded on printed or electronic case report forms (eCRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Details of study monitoring, including action required due to severe acute respiratory syndrome coronavirus 2 or coronavirus disease 2019, will be included in a separate Study Monitoring Plan.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study site's patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study site.

Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Clinical Monitoring Plan.

Study and Study Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of patients by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study site will be set forth in the Clinical Trial Agreement.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study site data. In this case, a Coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 3 Clinical Laboratory Tests

The tests detailed in [Table 5](#) will be performed by the central laboratories, [REDACTED] and The Doctors Laboratory (TDL). Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the electronic case report form (eCRF).

Protocol-specific requirements for inclusion or exclusion of patients are detailed in [Section 5.0](#) of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Investigators must document their review of each laboratory safety report. The results of each test must be entered into the eCRF.

Laboratory/analyte results that could unblind the study will not be reported to study sites or other blinded personnel until the study has been unblinded.

Table 5 Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	<u>RBC Indices:</u> Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes RBC morphology Red cell distribution (RDW)		<u>White Blood Cell Count with Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red Blood Cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry ^a	Blood Urea Nitrogen/Urea Uric acid	Potassium	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total, indirect, and direct bilirubin Gamma-glutamyltransferase (GGT) Albumin
	Creatinine (glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation)	Sodium Bicarbonate	Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein Lactate dehydrogenase (LDH)

Laboratory Assessments	Parameters
	<div> <div>Creatinine</div> <div>CCl</div> <div>Glucose</div> <div>Hemoglobin (HbA1c)</div> <div>kinase</div> <div></div> <div>A1c</div> <div>Calcium</div> <div>Alkaline phosphatase</div> </div>
Coagulation	Activated partial thromboplastin time, prothrombin time
Routine Urinalysis	<ul style="list-style-type: none"> Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)
Biomarkers	<p>Efficacy-related biomarkers</p> <ul style="list-style-type: none"> High-sensitivity cardiac troponin (hs-cTn) N-terminal pro B-type natriuretic peptide (NT-proBNP)^c <p>Exploratory biomarkers include the following:^d</p> <ul style="list-style-type: none"> CCl CCl Additional exploratory biomarkers may include the following: CCl <p>Immunogenicity</p> <ul style="list-style-type: none"> Anti-drug antibodies
<p>NOTES: All blood samples should be collected pre-dose at dosing days.</p> <p>a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1. All events of ALT $\geq 3 \times$ upper limit of normal (ULN) and bilirubin $\geq 2 \times$ ULN ($> 35\%$ direct bilirubin) or ALT $\geq 3 \times$ ULN and international normalized ratio (INR) > 1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).</p> <p>b Cystatin C will be analyzed at Day 1, Month 2, Month 3, and Month 6.</p> <p>c NT-proBNP values required for eligibility confirmation may be collected at any time post MI either through medical history (e.g., site has collected it as standard of care once the patient came to the hospital), through a local laboratory assessment, or by sending a sample to the central laboratory (if sites use the standard of care sample or the local laboratory sample for eligibility confirmation, no additional sample for central laboratory assessment is needed).</p> <p>d CCl</p>	

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

See [Section 8.4](#) for additional information regarding adverse events (AEs) and serious adverse events (SAEs).

Definition of AE

AE Definition
<ul style="list-style-type: none"> • An AE is any untoward medical occurrence in a patient or subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events <u>Meeting</u> the AE Definition
<ul style="list-style-type: none"> • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
<ul style="list-style-type: none"> Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening <ul style="list-style-type: none"> The term 'life-threatening' in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization <ul style="list-style-type: none"> In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d) Results in persistent disability/incapacity <ul style="list-style-type: none"> The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect

<ul style="list-style-type: none"> The term congenital anomaly/birth defect means there is suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
<p>f) Other situations:</p> <ul style="list-style-type: none"> Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording
<ul style="list-style-type: none"> When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE information in the electronic case report form (eCRF). Each event must be recorded separately. It is not acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor or designee in lieu of completion of the AE/SAE eCRF page. There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the Sponsor. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
<p>The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:</p> <ul style="list-style-type: none"> Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities. Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. <p>The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe); the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each AE recorded on the CRF</p>

Assessment of Causality
<ul style="list-style-type: none"> The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. <ul style="list-style-type: none"> Not related: An AE that does not follow a reasonable temporal sequence from administration of study drug(s), and/or that can be reasonably explained by other factors such as the subject's

preexisting medical condition, underlying disease, concurrent illness, or concomitant medications/therapies.

- **Related:** There is a reasonable possibility that an AE is caused by the study drug(s). A plausible temporal sequence exists between the time of administration of the study drug(s) and the development of the AE, or it follows a known response pattern to the study drug(s). The AE cannot be reasonably explained by the known characteristics of the subject's clinical state or other concomitant therapies, or interventions administered to the subject.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to the Sponsor via Paper SAE Report Form

- The primary mechanism for reporting an SAE to the Sponsor or designee will be the paper safety event report form. The site will submit the safety event report form, via email, within 24 hours of the Investigator's awareness of the event. Facsimile transmission may be utilized as an alternative mode of submission, if necessary.
- Notification of SAE information via telephone does not replace the need for the Investigator to complete, sign and submit the paper SAE report form to the Sponsor or designee within 24 hours of the Investigator's awareness of the event.
- Safety events should be reported to [REDACTED] at:
Email: [REDACTED]

[Redacted]

Phone:	[Redacted]
Fax:	[Redacted]

Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
 - a) Documented hysterectomy.
 - b) Documented bilateral salpingectomy.
 - c) Documented bilateral oophorectomy.

Note: Documentation can come from the study site personnel's: review of the patient's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
 - a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
 - b) Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male patients

Male patients with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in [Section 5.1](#):

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in [Table 6](#) when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

In addition, male patients must refrain from donating sperm for the duration of the study and for 30 days after the last dose of study treatment.

Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.

Table 6 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent^a <i>Failure rate of <1% per year when used consistently and correctly.</i>
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation ^b <ul style="list-style-type: none"> • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation <ul style="list-style-type: none"> • Oral. • Injectable.
Highly Effective Methods That Are User Independent^a
Implantable progestogen only hormonal contraception associated with inhibition of ovulation ^b <ul style="list-style-type: none"> • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). • Bilateral tubal occlusion.
Vasectomized Partner <i>A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.</i>
Sexual Abstinence <i>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.</i>
NOTES: ^a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies. ^b For WOCBPs in clinical trials hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the last dose of study treatment.

Collection of Pregnancy Information

Male patients with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive CDR132L.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Reporting Pregnancy Information

Email transmission of the paper Pregnancy Report Form is the preferred method to transmit safety event information to [REDACTED] with facsimile as a back-up method, if necessary.

Safety events should be reported to [REDACTED] at:

Email: [REDACTED]
Phone: [REDACTED]
Fax: [REDACTED]

Appendix 6 Signature of Investigator

PROTOCOL TITLE: Phase 2, Multicenter, Randomized, Parallel, 3-arm, Placebo-controlled Study to Assess Efficacy and Safety of CDR132L in Patients with Reduced Left Ventricular Ejection Fraction ($\leq 45\%$) After Myocardial Infarction (**HF-REVERT**)

PROTOCOL NO: CDR132L – P2-01

VERSION: Protocol Amendment 3.1

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study site in which the study will be conducted. Return the signed copy to Cardior Pharmaceuticals GmbH.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Site: _____
